EXHIBIT 36

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ORIGINAL ARTICLE

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

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ABSTRACT

BACKGROUND

The efficacy of thiazolidinediones, as compared with other oral glucose-lowering medications, in maintaining long-term glycemic control in type 2 diabetes is not known.

METHODS

We evaluated rosiglitazone, metformin, and glyburide as initial treatment for recently diagnosed type 2 diabetes in a double-blind, randomized, controlled clinical trial involving 4360 patients. The patients were treated for a median of 4.0 years. The primary outcome was the time to monotherapy failure, which was defined as a confirmed level of fasting plasma glucose of more than 180 mg per deciliter (10.0 mmol per liter), for rosiglitazone, as compared with metformin or glyburide. Prespecified secondary outcomes were levels of fasting plasma glucose and glycated hemoglobin, insulin sensitivity, and β-cell function.

RESULTS

Kaplan–Meier analysis showed a cumulative incidence of monotherapy failure at 5 years of 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. This represents a risk reduction of 32% for rosiglitazone, as compared with metformin, and 63%, as compared with glyburide ($P<0.001$ for both comparisons). The difference in the durability of the treatment effect was greater between rosiglitazone and glyburide than between rosiglitazone and metformin. Glyburide was associated with a lower risk of cardiovascular events (including congestive heart failure) than was rosiglitazone ($P<0.05$), and the risk associated with metformin was similar to that with rosiglitazone. Rosiglitazone was associated with more weight gain and edema than either metformin or glyburide but with fewer gastrointestinal events than metformin and with less hypoglycemia than glyburide ($P<0.001$ for all comparisons).

CONCLUSIONS

The potential risks and benefits, the profile of adverse events, and the costs of these three drugs should all be considered to help inform the choice of pharmacotherapy for patients with type 2 diabetes. (ClinicalTrials.gov number, NCT00279045.)

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THE ATTAINMENT AND MAINTENANCE of near-normal glycemia reduces the risk of long-term complications of diabetes.[1-3] Despite lifestyle and pharmacologic interventions, glucose levels increase over time in type 2 diabetes, probably as a consequence of declining β-cell function.[4] The progressive nature of type 2 diabetes makes it difficult to maintain target levels of glycated hemoglobin with traditional glucose-lowering agents[5,6] and generally necessitates the escalation of drug doses and the use of combination therapies or insulin.[7]

Thiazolidinediones reduce insulin resistance by sensitizing muscle, liver, and adipose tissue to insulin[8] and delay progression to type 2 diabetes in patients with glucose intolerance.[9-11] Small clinical studies have suggested that thiazolidinediones preserve β-cell function.[9,12] Thus, they may be of benefit as initial treatment of type 2 diabetes.

Our study, called A Diabetes Outcome Progression Trial (ADOPT), was a multicenter, randomized, double-blind, controlled clinical trial designed to evaluate the durability of glycemic control in patients receiving monotherapy with a thiazolidinedione, rosiglitazone (Avandia, GlaxoSmithKline); a biguanide, metformin (Glucophage, Bristol-Myers Squibb); or a sulfonylurea, glyburide (Micronase, Pfizer). All the patients in the study had not received previous pharmacologic treatment for type 2 diabetes that had been recently diagnosed (i.e., within 3 years). The primary outcome was the time to monotherapy failure on the basis of plasma glucose levels of more than 180 mg per deciliter (>10.0 mmol per liter) after an overnight fast. The trial permitted the direct comparison of the metabolic effects of these three commonly used glucose-lowering agents over an extended period.

METHODS

STUDY DESIGN

The ADOPT protocol, methods, and baseline characteristics of the cohort have been described previously.[13,14] Between April 2000 and June 2002, 4360 patients who had not received previous pharmacologic treatment for recently diagnosed type 2 diabetes were randomly assigned to receive double-blind monotherapy with one of the three study drugs (Fig. 1). Investigators at 488 centers in the United States, Canada, and 15 European countries participated in the study. Randomization was performed centrally and was concealed and stratified according to the sex of the patients in blocks of six. After the exclusion of 9 patients who did not receive a study drug, we evaluated 4351 patients in the safety analyses: 1456 in the rosiglitazone group, 1454 in the metformin group, and 1441 in the glyburide group. Of these patients, 224 (63 in the rosiglitazone group, 57 in the metformin group, and 104 in the glyburide group) withdrew before the first scheduled efficacy evaluation, which yielded a total of 4127 patients (95%) — including 1393 in the rosiglitazone group, 1397 in the metformin group, and 1337 in the glyburide group — for the intention-to-treat efficacy analyses.

The therapeutic goal was a fasting plasma glucose level below 140 mg per deciliter (7.8 mmol per liter). Patients were followed until the termination of the study in June 2006, with a median treatment duration of 4.0 years (maximum, 6.1).

PATIENTS

Eligible patients were between the ages of 30 and 75 years, with fasting plasma glucose levels ranging from 126 to 180 mg per deciliter (7.0 to 10.0 mmol per liter) while their only treatment was lifestyle management.[13] Exclusion criteria included clinically significant hepatic disease, renal impairment, a history of lactic acidosis, unstable or severe angina, known congestive heart failure (CHF, New York Heart Association class I, II, III, or IV), or uncontrolled hypertension.[13]

MONOTHERAPY ADMINISTRATION

In a double-blind regimen, patients received initial daily doses of 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide. All drugs were prepared in identical capsules to make them indistinguishable. For each drug, the dose was increased according to the protocol to the maximum daily effective dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). A dose increase was required at each visit if the fasting plasma glucose level was 140 mg per deciliter or more; a dose reduction was permitted if adverse events occurred.

BIOCHEMICAL AND CLINICAL MEASUREMENTS

Fasting plasma glucose levels were measured by hexokinase assay (Olympus America), and glycated

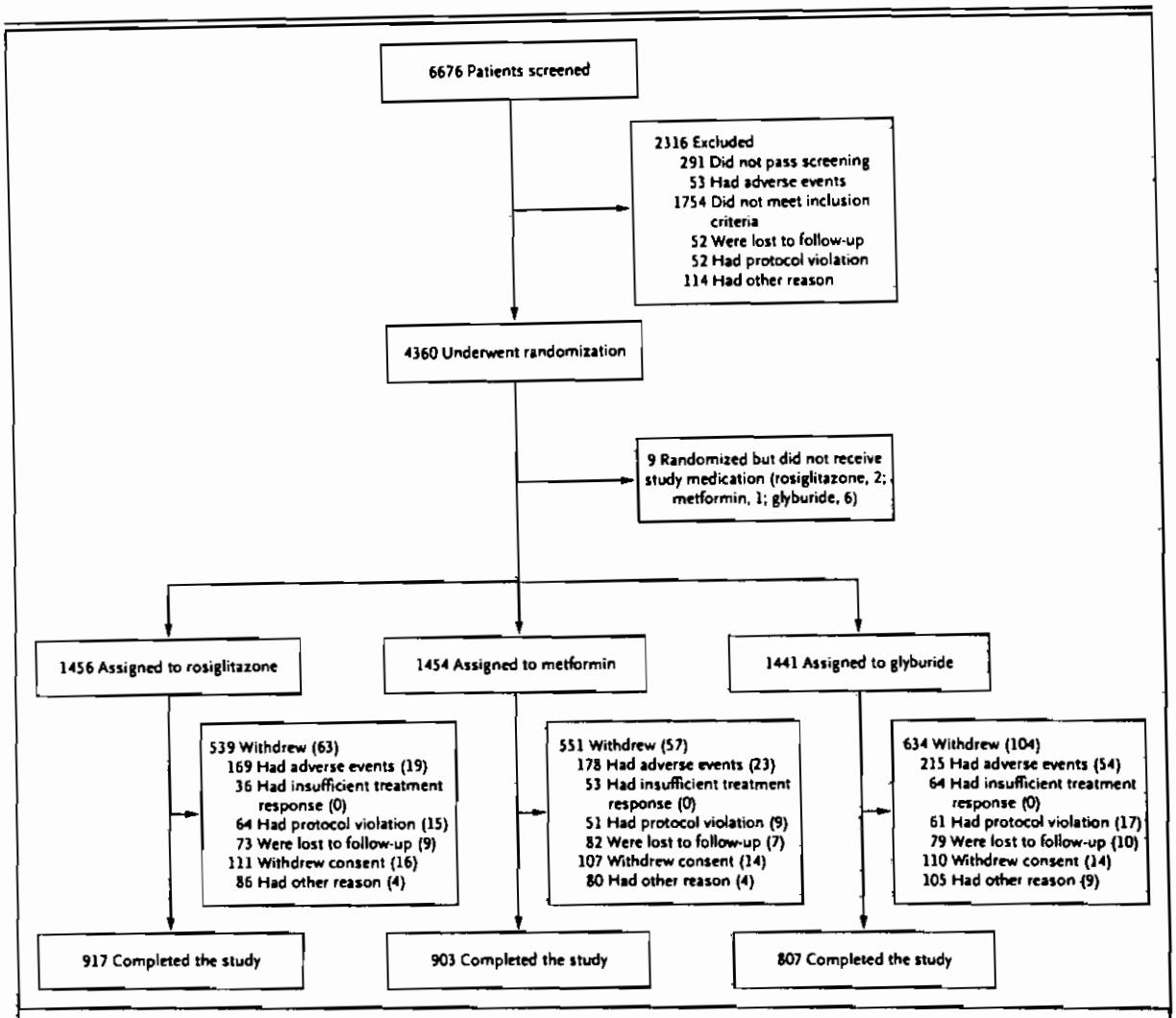


Figure 1. Enrollment and Outcomes.

The number of participants who were assessed for safety was 1456 in the rosiglitazone group, 1454 in the metformin group, and 1441 in the glyburide group. A total of 63 patients in the rosiglitazone group, 57 in the metformin group, and 104 in the glyburide group withdrew from the study before the first scheduled efficacy evaluation (as indicated by the numbers in parentheses), so the number of patients who were assessed for efficacy was 1393 in the rosiglitazone group, 1397 in the metformin group, and 1337 in the glyburide group.

hemoglobin by high-performance liquid chromatography (Biorad) every 2 months in the first year and every 3 months thereafter. Liver function tests, complete blood count, and measurements of immunoreactive insulin, C peptide, and lipids were performed at least annually. Blood samples were assayed in a central laboratory.[13] All study drugs were withheld on the morning of testing. Physical examination and electrocardiography were performed at baseline and annually.

OUTCOME MEASURES

The primary outcome was the time from randomization to treatment failure, which was defined as confirmed hyperglycemia (fasting plasma glucose level, >180 mg per deciliter) on consecutive testing after at least 6 weeks of treatment at the maximum-dictated or maximum-tolerated dose of the study drug. An independent adjudication committee, whose members were unaware of assignments to treatment groups, used prespecified

Table 1. Baseline Characteristics of the Patients.*

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Demographic characteristics			
Age — yr	56.3±10.0	57.9±9.9	56.4±10.2
Male sex — no. (%)	811 (55.7)	864 (59.4)	836 (58.0)
Race or ethnic background — no. (%)†			
White	1270 (87.2)	1295 (89.1)	1282 (89.0)
Black	61 (4.2)	54 (3.7)	61 (4.2)
Asian	39 (2.7)	35 (2.4)	32 (2.2)
Hispanic	76 (5.2)	55 (3.8)	61 (4.2)
Other	10 (0.7)	15 (1.0)	5 (0.3)
Region — no. (%)			
North America	758 (52.1)	758 (52.1)	758 (52.6)
Europe	698 (47.9)	696 (47.9)	683 (47.4)
Time since diagnosis of diabetes — no. (%)			
<1 yr	651 (44.6)	673 (46.3)	637 (44.2)
1–2 yr	758 (52.1)	724 (49.8)	751 (52.1)
>2 yr	47 (3.2)	57 (3.9)	53 (3.7)
Anthropometric characteristics			
Weight — kg	91.5±19.7	91.6±18.7	92.0±20.0
Body-mass index‡	32.2±6.7	32.1±6.1	32.2±6.3
Waist circumference — cm	105.3±14.6	105.6±14.3	105.6±15.1
Hip circumference — cm	111.4±14.1	111.2±13.4	111.8±14.2
Waist-to-hip ratio	0.95±0.09	0.95±0.10	0.94±0.09
Blood pressure			
Systolic — mm Hg	133±16	133±15	133±15
Diastolic — mm Hg	80±9	80±9	79±9
Antihypertensive therapy — no. (%)	744 (51.1)	737 (50.7)	753 (52.3)

criteria (see the Supplementary Appendix, available with the full text of this article at www.nejm.org) to determine whether the primary outcome was reached in cases in which a confirmatory fasting plasma glucose level had not been obtained, a patient had withdrawn because of an insufficient therapeutic effect, or an additional glucose-lowering drug had been administered before the confirmation of hyperglycemia (according to a protocol amendment adopted in February 2004). On the basis of the independent adjudication, treatment was deemed to have failed in 170 patients: 41 of the 143 patients who reached the primary end point (29%) in the rosiglitazone group, 61 of 207 (29%) in the metformin group, and 68 of 311 (22%) in the glyburide group.

The threshold of more than 180 mg per deciliter for confirmed hyperglycemia was selected to represent unequivocal failure in the maintenance of adequate glycemic control without incurring undue hyperglycemic symptoms; the threshold of a fasting plasma glucose level of more than 140 mg per deciliter for increasing the dose of a study drug reflected clinical guidelines at the time of study design.[15] The glycated hemoglobin level was not chosen as the primary outcome because guidelines at the initiation of the study focused largely on fasting plasma glucose levels.[15]

Prespecified secondary outcomes included the time from randomization to a confirmed fasting plasma glucose level of more than 140 mg per deciliter after at least 6 weeks of treatment at the maximum-tolerated dose of a study drug (for patients who entered the study with a fasting plasma

Table 1. (Continued.)

Variable	Rosiglitazone (N=1456)	Metformin (N=1454)	Glyburide (N=1441)
Metabolic characteristics			
Fasting plasma glucose — mg/dl	151.5±25.8	151.3±25.6	152.4±27.3
Glycated hemoglobin — %	7.36±0.93	7.36±0.93	7.35±0.92
Fasting insulin — pmol/liter	149.9±108.2	151.8±111.6	150.4±113.1
Insulin sensitivity — %§			
Median	33.8	33.3	33.1
Interquartile range	22.7–48.6	22.6–47.4	22.5–49.2
β-cell function — %§			
Median	68.0	69.5	67.9
Interquartile range	51.4–87.8	52.0–90.2	52.8–87.7
GAD positive — no. (%)¶	55 (4.0)	70 (5.1)	50 (3.6)
Lipids			
Total cholesterol — mg/dl			
Median	205	204	202
Interquartile range	177–231	177–231	177–230
LDL cholesterol — mg/dl‖			
Median	121	120	119
Interquartile range	98–144	96–143	98–144
HDL cholesterol — mg/dl			
Median	46.9	46.5	47.3
Interquartile range	39.0–54.6	39.6–55.0	39.0–55.4
Triglycerides — mg/dl			
Median	163	165	156
Interquartile range	116–230	112–233	112–222
Lipid-lowering therapy — no. (%)	378 (26.0)	377 (25.9)	370 (25.7)

* Plus–minus values are means ±SD. P>0.05 for all comparisons between treatment groups. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, and GAD glutamic acid decarboxylase. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

† Race or ethnic background was reported by the patients.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Insulin sensitivity and β-cell function were determined by homeostasis model assessment (HOMA 2) as a percentage of the values in a normal reference population, with the use of the HOMA Calculator (www.dtu.ox.ac.uk).

¶ GAD status was determined for 1388 patients in the rosiglitazone group, 1379 patients in the metformin group, and 1372 patients in the glyburide group.

‖ LDL cholesterol levels were calculated for patients with triglyceride levels of less than 400 mg per deciliter, including 1333 patients in the rosiglitazone group, 1340 patients in the metformin group, and 1342 patients in the glyburide group.

glucose level of 140 mg per deciliter or less). Other prespecified outcomes were levels of fasting plasma glucose and glycated hemoglobin, weight, and measures of insulin sensitivity and β-cell function,[16] as determined by homeostasis model assessment (HOMA 2) with the use of the HOMA Calculator (www.dtu.ox.ac.uk).

Site investigators reported all adverse events and collected data during the treatment period. At the end of the study, a cardiologist who was not connected with the study reviewed a listing of all serious adverse events. Cases suggestive of CHF were then evaluated by this practitioner and another independent cardiologist, both of whom were unaware of treatment assignments, to determine whether CHF was present. A third cardiologist arbitrated in case of disagreement. Site investigators were also asked to report deaths con-

sidered to be related to a study drug that occurred after the treatment period.

STUDY OVERSIGHT

The study protocol was approved by the institutional review board at each center, and all patients provided written informed consent. An independent data safety and monitoring board met twice a year to review unblinded safety data prepared by an independent statistical analysis group at the University of Wisconsin–Madison.

Study design, implementation, and analysis were performed under the supervision of the steering committee, which was composed of seven members from academic institutions and two from the sponsor, GlaxoSmithKline. The sponsor housed all blinded data during the treatment phase of the study and performed data analyses according to a prespecified plan developed with the academic biostatistician and approved by the steering committee. Independent academic statisticians confirmed key efficacy and safety results (see the Supplementary Appendix). Steering committee members, who had access to all data analyses and wrote the manuscript, attest to the veracity and completeness of the data. The decision to publish was made by the committee's academic members, with no restrictions imposed by the sponsor.

STATISTICAL ANALYSIS

We originally calculated that we would need to enroll 3600 patients to provide the study with a power of 90% to detect a 30% reduction in the risk of treatment failure for rosiglitazone, as compared with metformin and glyburide, at a significance level of $P=0.05$ (two-sided, adjusted for two comparisons), assuming an event rate of 0.072 per year for metformin or glyburide and a rate of loss to follow-up of 0.064 per year in each group. The protocol was amended in March 2002 to increase the number of patients to 4182 and in February 2004, to extend the follow-up period beyond 4 years, in order to compensate for an overall rate of withdrawal that was greater than anticipated and an overall rate of primary outcome events that was lower than anticipated. The revised power estimate was 83%, assuming a rate of loss to follow-up of 0.128 per year and a hazard rare for treatment failure of 0.035 per year.

The primary comparisons were rosiglitazone versus metformin and rosiglitazone versus glyburide. A secondary analysis compared metformin and glyburide. The percent reduction in risk was computed as 100 × (1 − the hazard ratio), with the hazard ratio estimated from the Cox proportional-hazards model. The cumulative incidence was estimated with the Kaplan–Meier method and with Gray's method, which adjusts for deaths.[17] Two-sided nominal P values are reported for all comparisons. The Hochberg method was used to determine statistical significance at the 0.05 level, adjusted for two comparisions.[17] Other details about the statistical methods used in the study are available in the Supplementary Appendix.

RESULTS

BASELINE CHARACTERISTICS AND FOLLOW-UP

Of the 6676 subjects who were initially screened, 4360 were randomly assigned to the three treatment groups (Fig. 1). Patients were middle-aged, predominantly white, and obese (body-mass index [the weight in kilograms divided by the square of the height in meters], >30), with no significant differences in baseline variables among the groups (Table 1). The median duration of treatment was 4.0 years for rosiglitazone and metformin and 3.3 years for glyburide. The proportion of patients who either reached the primary outcome or completed the study was 63% in the rosiglitazone group, 62% in the metformin group, and 56% in the glyburide group. The primary reasons that patients did not complete the study were adverse events (12% of patients in the rosiglitazone group, 12% in the metformin group, and 15% in the glyburide group; $P<0.001$ for the comparison between the rosiglitazone group and the glyburide group) and withdrawal of consent (7 to 8% of patients in all three groups). The demographic, anthropometric, and metabolic characteristics of patients who withdrew from the study did not differ significantly among treatment groups.

PRIMARY OUTCOME

Monotherapy failed in 143 patients who received rosiglitazone (2.9 per 100 patient-years), 207 who received metformin (4.3 per 100 patient-years), and 311 who received glyburide (7.5 per 100 patient-years). The Kaplan–Meier cumulative incidence at 5 years was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide (Fig. 2). The risk (incidence) was reduced by 32% (95% con-

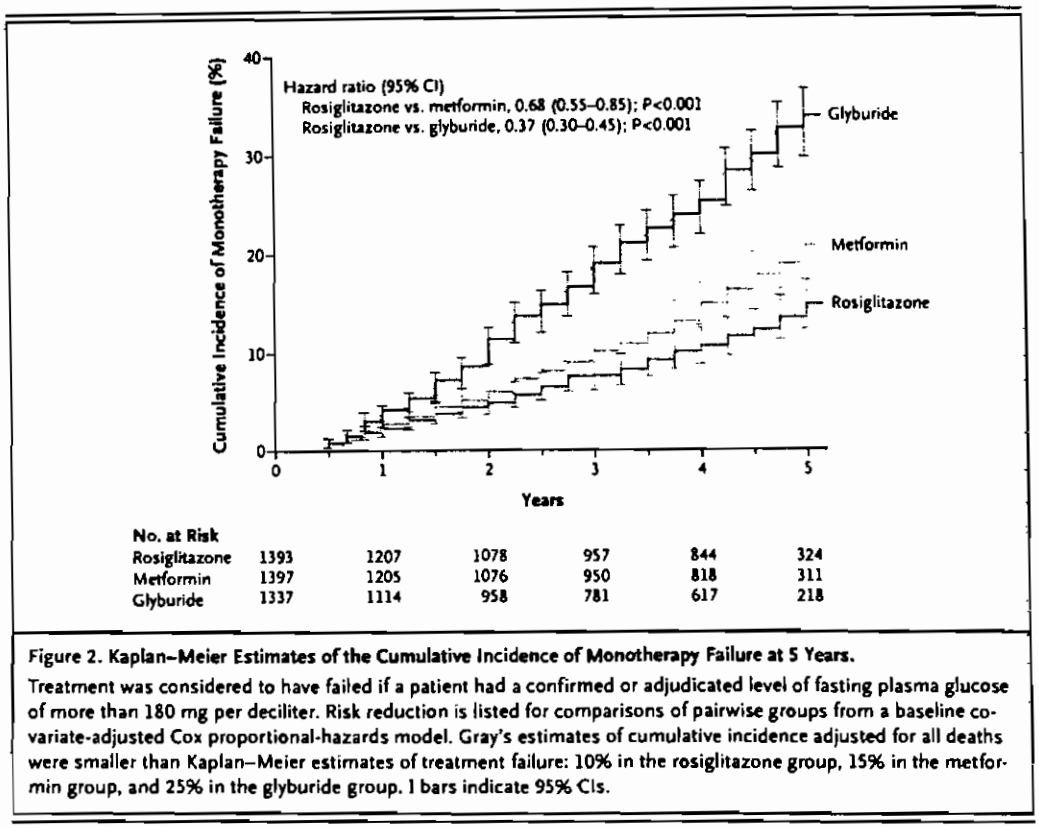


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Monotherapy Failure at 5 Years.

Treatment was considered to have failed if a patient had a confirmed or adjudicated level of fasting plasma glucose of more than 180 mg per deciliter. Risk reduction is listed for comparisons of pairwise groups from a baseline covariate-adjusted Cox proportional-hazards model. Gray's estimates of cumulative incidence adjusted for all deaths were smaller than Kaplan–Meier estimates of treatment failure: 10% in the rosiglitazone group, 15% in the metformin group, and 25% in the glyburide group. I bars indicate 95% CIs.

fidence interval [CI], 15 to 45) with rosiglitazone as compared with metformin and by 63% (95% CI, 55 to 70) with rosiglitazone as compared with glyburide (P<0.001 for both comparisons).

At the time of treatment failure, 99.3% of patients in the rosiglitazone group, 98.6% in the metformin group, and 99.0% in the glyburide group were receiving the maximum dose of the study drug. A sensitivity analysis indicated that the benefit of rosiglitazone, as compared with glyburide, was probably not attributable to bias caused by early withdrawal from the study, but this factor could not be excluded for the comparison of rosiglitazone and metformin (see the Supplementary Appendix). Subgroup analyses suggested that the treatment effect was greater with rosiglitazone than with metformin among older patients (≥50 years of age) and among those with a larger waist circumference (>110 cm) (Fig. 3). Rosiglitazone was more effective than glyburide in all subgroups.

For treatment failure not requiring adjudication, the findings were similar to those for the primary outcome: treatment failed in 102 patients in the rosiglitazone group, as compared with 146 patients in the metformin group (risk reduction, 31%; 95% CI, 11 to 46; P=0.004) and 243 patients in the glyburide group (risk reduction, 66%; 95% CI, 57 to 73; P<0.001).

SECONDARY OUTCOMES

The rate of progression to a confirmed fasting plasma glucose level of more than 140 mg per deciliter also differed significantly among the groups: 79 of 511 patients in the rosiglitazone group, as compared with 127 of 520 patients in the metformin group (risk reduction, 36%; 95% CI, 15 to 52; P=0.002) and 160 of 480 patients in the glyburide group (risk reduction, 62%; 95% CI, 51 to 72; P<0.001) (Fig. 1 of the Supplementary Appendix).

Within the first 6 months, levels of fasting plasma glucose and glycated hemoglobin decreased in all treatment groups, with glyburide showing the greatest effect (Fig. 4A and 4B). After 6 months, the rates of increase in these glycemic measures

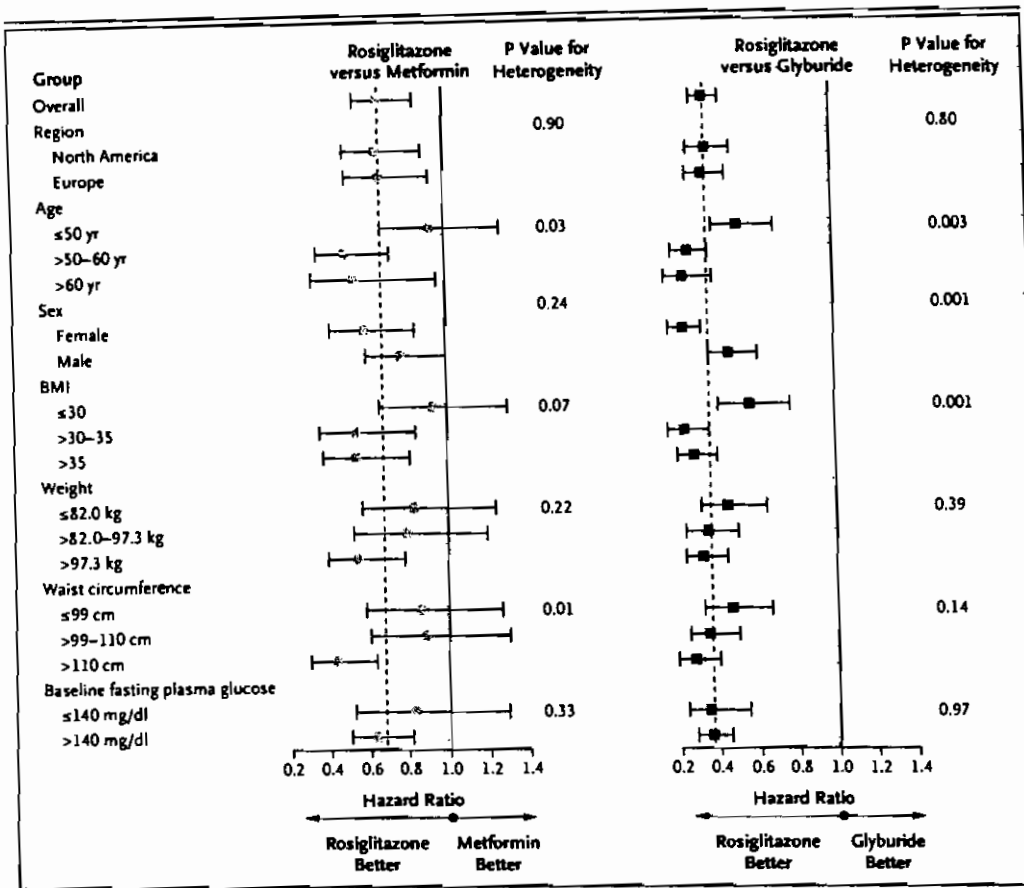


Figure 3. Hazard Ratio for Monotherapy Failure in the Rosiglitazone Group, as Compared with the Metformin and Glyburide Groups in Key Subgroups.

The test for heterogeneity (interaction) indicates whether the treatment effect varied significantly among the subgroups. The Hochberg method was applied to each of the two comparisons of the treatment groups. BMI denotes body-mass index (the weight in kilograms divided by the square of the height in meters).

were greatest in the glyburide group, which had annual increases of 5.6 mg per deciliter (0.31 mmol per liter) in the fasting plasma glucose level and 0.24% in the glycated hemoglobin level ($P<0.001$ for the comparisons of both values with those in the rosiglitazone group); intermediate in the metformin group, which had annual increases of 2.7 mg per deciliter (0.15 mmol per liter) in the fasting plasma glucose level and 0.14% in the glycated hemoglobin level ($P<0.001$ for the comparisons of both values with those in the rosiglitazone group); and least in the rosiglitazone group, which had increases of 0.7 mg per deciliter (0.04 mmol per liter) in the fasting plasma glucose level and 0.07% in the glycated hemoglobin level. A worst-rank sensitivity analysis, performed to evaluate the effect of early withdrawal of patients because of either treatment failure or insufficient therapeutic effect, showed that withdrawals did not significantly influence the results (Fig. 2 of the Supplementary Appendix).

At the 4-year evaluation, 40% of the 1456 patients in the rosiglitazone group had a glycated hemoglobin level of less than 7%, as compared with 36% of the 1454 patients in the metformin group ($P=0.03$) and 26% of the 1441 patients in the glyburide group ($P<0.001$). The maximal treatment effect on glycated hemoglobin was achieved at 12 months for patients in the rosiglitazone and metformin groups and at 4 months for those in the glyburide group. From the longitudinal linear model, a mean glycated hemoglobin level of less

than 7% was maintained until the visit at 57 months in the rosiglitazone group, at 45 months in the metformin group, and at 33 months in the glyburide group (Fig. 4B).

As compared with glyburide, metformin was associated with a reduction in the risk of monotherapy failure of 46% (95% CI, 36 to 55; P<0.001) and a reduction in the risk of exceeding a fasting plasma glucose level of 140 mg per deciliter of 41% (95% CI, 25 to 54; P<0.001). At 4 years, metformin, as compared with glyburide, was associated with a reduction in the mean fasting plasma glucose level of 7.6 mg per deciliter (95% CI, 4.6 to 10.6) (0.42 mmol per liter [95% CI, 0.26 to 0.59]; P<0.001) and a reduction in the glycated hemoglobin level of 0.28% (95% CI, 0.20 to 0.37; P<0.001).

During the first 6 months, insulin sensitivity (as determined by HOMA) increased more in the rosiglitazone group (mean ratio of the 6-month value to the baseline value, 1.30; 95% CI, 1.28 to 1.34) than in the metformin group (mean ratio, 1.17; 95% CI, 1.15 to 1.20). Thereafter, insulin sensitivity improved at similar rates in the two groups, with a significant difference between the two groups at 4 years (P<0.001) (Fig. 4C). Insulin sensitivity did not change significantly in the glyburide group.

During the first 6 months, levels of β-cell function (as determined by HOMA) increased more in the glyburide group (mean ratio of 6-month value to baseline value, 1.45; 95% CI, 1.42 to 1.48) than in either the rosiglitazone group (1.17; 95% CI, 1.15 to 1.19) or the metformin group (1.16; 95% CI, 1.14 to 1.19) (Fig. 4D). Thereafter, levels of β-cell function declined in all three groups. The annual rate of decline after 6 months was greatest in the glyburide group (a decrease of 6.1%), intermediate in the metformin group (a decrease of 3.1%), and least in the rosiglitazone group (a decrease of 2.0%) (P<0.001 for the comparison of the rosiglitazone group and the glyburide group and P=0.02 for the comparison of the rosiglitazone group and the metformin group).

Over a period of 5 years, the mean weight increased in the rosiglitazone group (change from baseline, 4.8 kg; 95% CI, 4.3 to 5.3) but decreased in the metformin group (−2.9 kg; 95% CI, −3.4 to −2.3) (Fig. 4E). In the glyburide group, weight gain occurred in the first year (1.6 kg; 95% CI, 1.0 to 2.2), then remained stable. Changes in waist and hip circumferences and waist-to-hip ratio over time are shown in Figures 4F, 4G, and 4H.

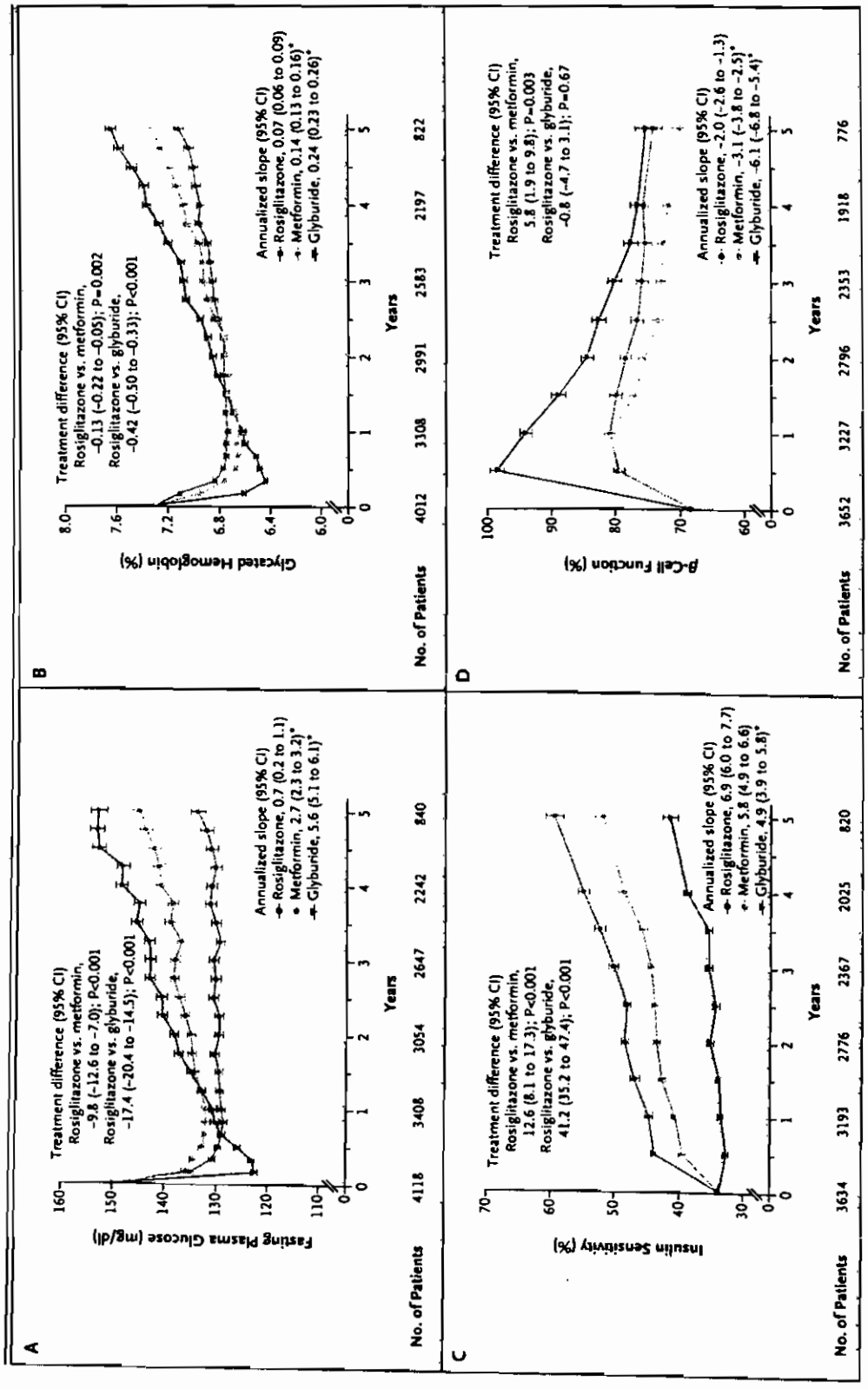
ADVERSE EVENTS, LABORATORY MEASURES, AND CONCOMITANT MEDICATIONS

The number of deaths from all causes was similar in the three groups. However, adverse events differed among the groups (Table 2). Cardiovascular events were reported in 62 patients in the rosiglitazone group, 58 in the metformin group, and 41 in the glyburide group. For all investigator-reported CHF events, 22 occurred in the rosiglitazone group (1.5%), 19 in the metformin group (1.3%), and 9 in the glyburide group (0.6%). The hazard ratio for CHF in the rosiglitazone group, as compared with the metformin group, was 1.22 (95% CI, 0.66 to 2.26; P=0.52); the hazard ratio for the rosiglitazone group, as compared with the glyburide group, was 2.20 (95% CI, 1.01 to 4.79; P=0.05). Episodes of CHF classified as serious adverse events occurred in 12 patients in the rosiglitazone group, 12 in the metformin group, and 3 in the glyburide group.

The independent cardiology review of all serious adverse events identified 51 possible CHF events. Of these, 21 were judged to be true CHF, involving 9 patients in the rosiglitazone group, 8 in the metformin group (with 1 death), and 4 in the glyburide group (with 1 death) (P=0.26 for the comparison between the rosiglitazone group and the glyburide group). No patient was determined to have had more than one CHF event.

Rosiglitazone was more frequently associated with edema and the use of loop diuretics than was either metformin or glyburide (P<0.001 for both comparisons). Rosiglitazone was less frequently associated with gastrointestinal side effects than was metformin (P<0.001), and fewer patients in the rosiglitazone group than in the glyburide group had hypoglycemia (P<0.001).

Levels of alanine aminotransferase decreased significantly from baseline in the rosiglitazone group, remained stable in the metformin group (P<0.001 for the comparison with the rosiglitazone group), and increased significantly from baseline in the glyburide group (P<0.001 for the comparison with the rosiglitazone group) (Table 2). Treatment with rosiglitazone was associated with a significantly decreased hematocrit, as compared with both metformin and glyburide (P<0.001 for both comparisons). Rosiglitazone was associated with significantly higher levels of low-density lipoprotein (LDL) cholesterol than were the other two drugs (P<0.001 for the comparison with metformin and P=0.008 for the comparison with



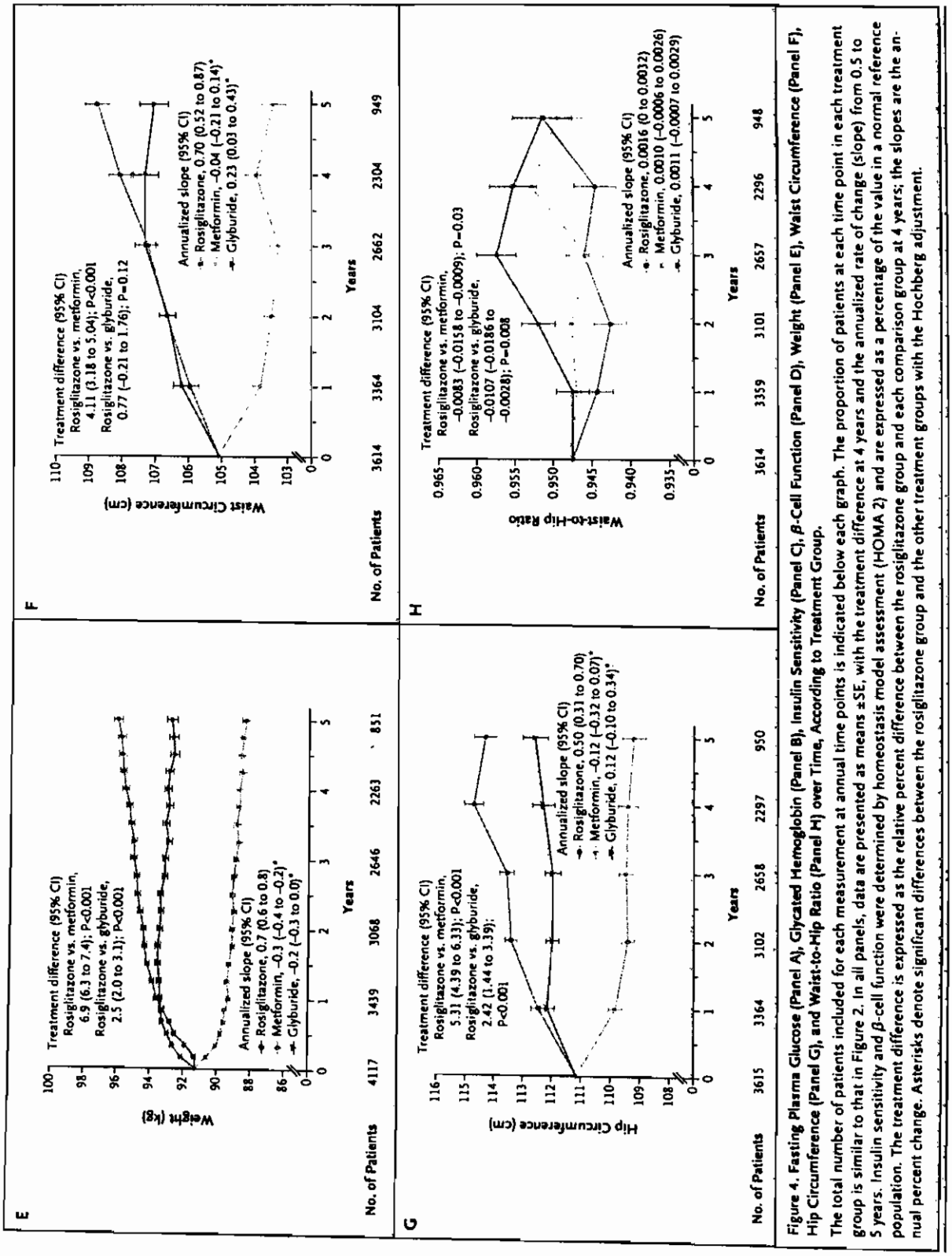


Figure 4. Fasting Plasma Glucose (Panel A), Glycated Hemoglobin (Panel B), Insulin Sensitivity (Panel C), β-Cell Function (Panel D), Weight (Panel E), Waist Circumference (Panel F), Hip Circumference (Panel G), and Waist-to-Hip Ratio (Panel H) over Time, According to Treatment Group.

The total number of patients included for each measurement at annual time points is indicated below each graph. The proportion of patients at each time point in each treatment group is similar to that in Figure 2. In all panels, data are presented as means ±SE, with the treatment difference at 4 years and the annualized rate of change (slope) from 0.5 to 5 years. Insulin sensitivity and β-cell function were determined by homeostasis model assessment (HOMA 2) and are expressed as a percentage of the value in a normal reference population. The treatment difference is expressed as the relative percent difference between the rosiglitazone group and each comparison group at 4 years; the slopes are the annual percent change. Asterisks denote significant differences between the rosiglitazone group and the other treatment groups with the Hochberg adjustment.

Table 2. Adverse Events, Laboratory Assessment, Concomitant Use of Cardiovascular Drugs, Hospitalization, and Death.*

Variable	Rosiglitazone (N=1456)		Metformin (N=1454)		Glyburide (N=1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
Adverse events — no. of patients (%)						
Total events	346 (23.8)	1338 (91.9)	331 (22.8)	1341 (92.2)	308 (21.4)	1321 (91.7)
Cardiovascular disease	49 (3.4)	62 (4.3)	46 (3.2)	58 (4.0)	26 (1.8)†	41 (2.8)
Myocardial infarction						
Fatal	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)	3 (0.2)	3 (0.2)
Nonfatal	22 (1.5)	25 (1.7)	18 (1.2)	21 (1.4)	11 (0.8)	15 (1.0)
Congestive heart failure (investigator-reported)	12 (0.8)	22 (1.5)	12 (0.8)	19 (1.3)	3 (0.2)†	9 (0.6)†
Stroke	13 (0.9)	16 (1.1)	17 (1.2)	19 (1.3)	12 (0.8)	17 (1.2)
Peripheral vascular disease	7 (0.5)	36 (2.5)	6 (0.4)	27 (1.9)	4 (0.3)	31 (2.2)
Gastrointestinal events	8 (0.5)	335 (23.0)	7 (0.5)	557 (38.3)‡	3 (0.2)	316 (21.9)
Nausea	2 (0.1)	112 (7.7)	0	170 (11.7)‡	0	99 (6.9)
Vomiting	0	58 (4.0)	1 (0.1)	84 (5.8)†	0	45 (3.1)
Diarrhea	1 (0.1)	129 (8.9)	1 (0.1)	345 (23.7)‡	0	142 (9.9)
Abdominal discomfort	5 (0.3)	161 (11.1)	6 (0.4)	224 (15.4)‡	3 (0.2)	163 (11.3)
Hypoglycemia§	1 (0.1)	142 (9.8)	1 (0.1)	168 (11.6)	8 (0.6)†	557 (38.7)‡
Weight gain	3 (0.2)	100 (6.9)	0	18 (1.2)‡	0	47 (3.3)‡
Edema	2 (0.1)	205 (14.1)	0	104 (7.2)‡	2 (0.1)	123 (8.5)‡
Laboratory assessment¶						
ALT — IU/liter						
Mean	21.4		24.9‡		27.2‡	
95% CI	20.6–22.2		24.1–25.8		26.3–28.1	
ALT >3 times upper limit of normal — no. of patients (%)	14 (1.0)		16 (1.1)		11 (0.8)	
Hematocrit — %						
Mean	40.6		41.6‡		42.7‡	
95% CI	40.4–40.8		41.4–41.8		42.5–42.9	
Hematocrit ≥5 percentage points below the reference range — no. of patients (%)	41 (2.8)		22 (1.5)†		14 (1.0)‡	
LDL cholesterol — mg/dl						
Mean	104.0		96.5‡		99.3‡	
95% CI	101.7–106.4		94.4–98.8		96.9–101.9	

glyburide) and with greater use of lipid-lowering therapy.

DISCUSSION

Our international clinical trial suggests that initial treatment of type 2 diabetes with rosiglitazone during a median period of 4 years slowed progression to monotherapy failure (defined as a fasting plasma glucose level >180 mg per deciliter) more effectively than did either metformin or glyburide. This was also the case with a lower threshold for monotherapy failure (fasting plasma glucose level, >140 mg per deciliter), a level more consistent with that used in current therapeutic approaches to glucose management.[18,19] Although rosiglitazone was more effective overall than metformin, heterogeneity analyses showed no subgroup differences apart from a greater effect in older patients and those with a larger waist circumference.

When we designed our study, measurement of

Table 2. (Continued.)

Variable	Rosiglitazone (N = 1456)		Metformin (N = 1454)		Glyburide (N = 1441)	
	Serious Events	Total Events	Serious Events	Total Events	Serious Events	Total Events
HDL cholesterol — mg/dl						
Mean	51.8		50.5‡		48.9‡	
95% CI	51.3–52.4		50.0–51.0		48.3–49.5	
Triglycerides — mg/dl						
Mean	163.5		166.5		171.7†	
95% CI	159.2–167.9		162.1–171.0		166.8–176.9	
Drugs used concomitantly — no. of patients (%)						
Lipid-lowering agents	803 (55.2)		708 (48.7)‡		651 (45.2)‡	
Statins	750 (51.5)		632 (43.5)‡		579 (40.2)‡	
Antihypertensive agents	970 (66.6)		969 (66.6)		944 (65.5)	
ACE inhibitors	559 (38.4)		607 (41.7)		538 (37.3)	
Angiotensin receptor blockers	259 (17.8)		293 (20.2)		280 (19.4)	
Beta-blockers	406 (27.9)		398 (27.4)		379 (26.3)	
Calcium channel blockers	271 (18.6)		276 (19.0)		286 (19.8)	
Diuretics						
Loop	214 (14.7)		162 (11.1)‡		160 (11.1)‡	
Potassium sparing	90 (6.2)		91 (6.3)		93 (6.5)	
Thiazide	394 (27.1)		369 (25.4)		349 (24.2)	
Death and hospitalization						
Hospitalization for any cause						
Patients — no. (%)	169 (11.6)		172 (11.8)		150 (10.4)	
Events — no.	251		267		203	
Deaths from any cause — no.	34		31		31	

* The total number of patients with adverse events includes all patients with serious events reported by investigators. All deaths were reported, regardless of whether the patient died during or after treatment. A serious adverse event was defined as any event that was fatal, life-threatening, or disabling; resulted in hospitalization or prolonged a hospital stay; was associated with a congenital abnormality, cancer, or a drug overdose (either accidental or intentional); or was regarded by the investigator as serious or suggested any substantial hazard, contraindication, side effect, or precaution. Tests of differences between means of laboratory assessments were conducted by linear model analysis after 4 years of follow-up. Comparisons for cardiovascular disease events in aggregate and by type, as well as for peripheral vascular disease, were calculated by the Cox proportional-hazards model to allow for differential time of follow-up among treatments. Comparisons for other events were based on the test for proportions. ALT denotes alanine aminotransferase, LDL low-density lipoprotein, HDL high-density lipoprotein, and ACE angiotensin-converting enzyme. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

† $P \leq 0.05$ for the comparison between this treatment group and the rosiglitazone group.

‡ $P \leq 0.01$ for the comparison between this treatment group and the rosiglitazone group.

§ Patients self-reported hypoglycemia at the time of a follow-up visit, although levels were not necessarily confirmed by glucose testing.

¶ All laboratory values are mean values at 4 years.

glycated hemoglobin was not in general use for the adjustment of glucose-lowering therapy.[15] Nevertheless, systematic and prespecified collection of data regarding glycated hemoglobin levels provided results applicable to current clinical practice. By comparing three drugs head to head, our study provides long-term evidence that progressive loss of glycemic control can be delayed and a mean level of glycated hemoglobin maintained at less than 7% for a longer period with rosiglitazone (57 months) than with either metformin (45 months) or glyburide (33 months). Our findings confirm the value of metformin as an initial treatment for type 2 diabetes[20] and the greater efficacy of metformin than of glyburide.

Declining β-cell function is the predominant reason for deterioration in glucose tolerance across the spectrum from normal glucose tolerance to

type 2 diabetes in numerous populations.[21-23] In the United Kingdom Prospective Diabetes Study (UKPDS), neither metformin nor a sulfonylurea altered the rate of loss of β-cell function, although metformin improved insulin sensitivity.[4] In our study, rosiglitazone slowed the rate of loss of β-cell function and improved insulin sensitivity to a greater extent than did either metformin or glyburide. These complementary findings are consistent with a greater durability of glycemic control with rosiglitazone.[24]

There were no unexpected adverse events in any of the treatment groups. Rosiglitazone was associated with weight gain, increased levels of LDL cholesterol (and more use of statins), more frequent edema, and a reduction in the hematocrit. Metformin was associated with more frequent gastrointestinal side effects, and glyburide with weight gain and hypoglycemia. An increase from baseline in waist circumference was observed with rosiglitazone and glyburide, but the concomitant increase in hip circumference with rosiglitazone resulted in no net change in the waist-to-hip ratio.[11] Redistribution of body fat[25,26] and varying patterns of adipokine release[27,28] may explain the improved insulin sensitivity observed with rosiglitazone, despite the increase in weight. The long-term health effect of increases in weight and changes in body composition with thiazolidinediones should be further explored.

Our study was not designed to evaluate cardiovascular disease outcomes. The protocol specified that all patients be free of known CHF on entry into the study. However, a retrospective review of source documents revealed that 17 patients (5 in the rosiglitazone group, 6 in the metformin group, and 6 in the glyburide group) entered the study with a current diagnosis of CHF. Only one of these patients (randomized to metformin) contributed to the events of CHF that are detailed in Table 2. Overall, the proportions of patients with cardiovascular events were similar in the rosiglitazone and metformin groups but were lower in the glyburide group. This observation differs from the UKPDS findings, which suggested that metformin reduces overall mortality and may reduce coronary events.[20] This difference may be related to the facts that our study had a shorter follow-up period than did the British study and that our patients were younger and had better glycemic control at study entry. Furthermore, our definition of treatment failure (a fasting plasma glucose level of more than 180 mg per deciliter) was lower than that in the British study (270 mg per deciliter [15 mmol per liter]).[3] The lower rate of cardiovascular events associated with glyburide also differs from epidemiologic studies suggesting an increase in the rates of death and myocardial infarction with sulfonylureas.[29,30]

Since thiazolidinediones have been associated with an increased risk of CHF,[11,31,32] we specifically examined serious adverse events that were potentially related to this risk. The rate of CHF associated with rosiglitazone was similar to that in studies involving low-risk populations[11,31] and to that associated with metformin but higher than that associated with glyburide.

The rate of withdrawal of patients from our study was high, which was a limitation of the study. However, the characteristics of patients who withdrew did not differ among the treatment groups. Many withdrawals resulted from well-characterized side effects of each drug. Although the groups differed with respect to the number of withdrawals prompted by an insufficient therapeutic effect, these differences were small, as compared with the number of patients reaching the primary outcome. The groups did not differ significantly in the number of patients who withdrew because of protocol violations, were lost to follow-up, or withdrew consent. Furthermore, analyses that accounted for the potential bias introduced by early withdrawal provided consistent results, indicating that the findings were robust.

Whether the statistically significant differences between rosiglitazone and metformin would translate into longer-term effects on disease progression or on microvascular or macrovascular outcomes needs to be determined. Taken together, the data from our study document the glycemic durability and risks associated with three commonly used drugs in the initial management of type 2 diabetes. The relative costs of these medications, their profiles of adverse events, and their potential risks and benefits should all be considered to help inform the choice of pharmacotherapy for patients with type 2 diabetes.

Note added in proof: While this article was in production, further examination of data on adverse events identified a higher rate of fractures in the group receiving rosiglitazone. This was an unexpected event that was not part of the prespecified analysis plan.

	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

* P<0.01 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).
† P<0.05 for the comparison with rosiglitazone (unadjusted, contingency chi-square test).

The number of men with fractures did not differ according to the treatment group. More women in the rosiglitazone group had upper limb fractures involving the humerus and hand. Lower limb fractures were primarily increased in the foot. Specifically, the number of women with hip fractures did not differ (two patients receiving rosiglitazone, two receiving metformin, and none receiving glyburide).

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APPENDIX

The following participated in the ADOPT study: *Steering Committee* — S. Kahn, G. Viberti (co-chairs), S. Haffner, W. Herman, R. Holman, N. Jones, J. Lachin, C. O'Neill, B. Zinman; *Data and Safety Monitoring Board* — A. Garber, M. Fisher (co-chairs), H. Dargie, J. Fuller; *Safety Analysis Group at University of Wisconsin, Madison* — E. Roecker, T. Havighurst; *Adjudication Committee* — M. Abrahamson (chair), D. Kelley, J.-F. Yale; *ADOPT Study Management Team* —A. Phillips, M. Freed, C. O'Neill, B. Kravitz, D. Yu, R. Fowler, K. Saarinen, D. Steele-Norwood, K. Huckel, A. Cobitz, B. Louridas, C. Kirsch, J. Balcarek, A. Wolstenholme; *ADOPT Statistics and Data Management Team* — M. Heise, G. Paul, J. Koskinas, A. McClatchy, P. Stober, C. Weikert, D. Wade, J. Wang; Investigators — *Austria* — R. Prager, H. Abrahamian, B. Ludvik, K. Mihajlevic, R. Lober, N. Scharf; *Belgium* — E. Muls, C. Mathieu, G. Watté, G. Vileyn, G. Mehuys, R. Leliaert, P. Roelands, S. Bresseleers, F. Heyvaert, W. Van Peer, J. Verelst, R. Wouters, G. Vandistel, G. Dedeyne, H. Morobé, M. Carpentier, A. Ceusters; *Canada* — R. Aronson, C. Halyk, G. Bailey, A. Hollingshead, A. Bélanger, M. Meilleur, J. Berlingieri, F. Petrie, M. Boctor, M. Pole, W. Booth, F. Landry, J. Bouchard, L. Morin, R. Cheung, D. St. Louis, G. Costain, D. Tweel, M. Ferguson, K. Dawson, J. Lewis, J. Ekoé, J. DesCormiers, P. Filteau, G. Janelle, P. Fournier, L. Piuze, C. Garceau, D. Trudel, D. Gaudet, P. Perron, L. Côté, R. Goldenberg, S. Code, T. Coady-MacKinnon, I. Gottesman, D. Hasler, J. Hallé, A. Toupin, P. Hardin, B. Sternberg, R. Houlden, T. LaVallee, I. Hramiak, S. Powers, C. Kovacs, D. Gibbons, C. Lai, G. Fox, R. LaMontagne, H. LaMontagne, D. Lau, M. Clearwaters, L. Leiter, D. Bedard, S. Ludwig, S. Erickson-Nesmith, M. MacSween, B. Cole, P. Maheux, P. Perron, M. Luc, S. Mann, S. Brown, L. Murphy, L. Berard, T. Ooi, C. Favreau, A. Parent, M. Blais, M. Parmar, J. Bradley, E. Ryan, M. Pick, D. Shu, S. Prieur, E. Ur, T. Palmer, L. van den Berg, R. Brown, T. Zmijowskyj, B. Ward; *Czech Republic* — T. Pelikánová, A. Jirkovská, R. Šimková, V. Fejfarová, M. Kvapil, D. Bartášková, D. Žárská, F. Pátek, N. Shorná, J. Rybka, L. Švestka, M. Honka, A. Navrátilová; *Denmark* — H. Beck-Nielsen, I. Jacobsen, K. Koelendorf; *Finland* — J. Eriksson, T. Forsén, M. Vanhala, J. Starck, J. Saramies, T. Hurskainen, J. Saltevo, U. Venesmaa, T. Hellsten, M. Söderlund-Sarpoma; *France* — P. Blanchard, J. Leclaire, G. Lalanne, J. Gaube, F. Leroy-Duroure, R. Soullard, C. Faugere, D. Lacoume, Y. Mercey, R. Moreno, B. Pellenq, P. Roche, J.-N. Nal, R. Fonteny, P. Poisson, D. Sacareau, M. Bismuth, G. Sorbé, Y. Foure, P. Causse, D. Lecaignard, C. Scellier, J.-P. Enrione-Thorrand, D. Cadinot, G. Tellier, F. Lacoin, J.-C. Deme, J.-L. Rosé, L. Esquerre, S. Farhat, G. Ronzières, N. Breton, P. Jaudon, N. Abenhaim, S. Rosenberg, F. Spilthooren, B. Pairin, A. Boye, L. Formagne, D. Lejay, M. Herent, J. Marty, S. Faligot, B. Chagnoux, G. Constantin, A. El Sawy, J.-P. Allamanno, A. Duplan, M. Fleury, L. Boucher, D. Marin, G. Faugas, J.-J. Vanpraet, E. De Sainte Lorette, J.-C. Mouchet, T. Latte, D. Diard, P. Esteve, B. Lafaurie, A. Dyan, M. Braud, J. Dupouy, M. Chay, J.-M. Letzeltzer,

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CORRECTION

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy . Having discovered an error in their original reporting, the authors undertook a complete audit of all the data reported in the published article. The results of that audit change some of the published data, as follows. None of these changes materially affect the scientific findings, interpretation, or conclusions of the study. In the Methods section, the last sentence under Study Design (page 2428) should heve read "Patients were followed until the termination of the study in June 2006, with a median treetment duration of 4.0 yeers (maximum, 6.1)," rather than "(maximum, 6.0)." In Table 1 (page 2430), in the "Time since diagnosis of diabetes" entry, the number of rosiglitazone patients should have been 651 for <1 year and 758 for 1–2 years. In the Results section, the first sentence under Secondary Outcomes (page 2433) should have read "The rate of progression to a confirmed fasting plasme glucose level of more then 140 mg per deciliter also differed significantly among the groups: 79 of 511 patients in the rosiglitazone group, as compered with 127 of 520 patients in the metformin group (risk reduction, 36%; 95% CI, 15 to 52; P=0.002)," rether than "risk reduction, 34%." In Figure 3 (page 2434), the ranges should have been as follows: Age: ≤50 yr, >50–60 yr, >60 yr; BMI: ≤30, >30–35, >35; Weight: ≤82.0 kg, >82.0–97.3 kg, >97.3 kg; Waist circumferance: ≤99 cm, >99–110 cm, >110 cm; and Baseline fasting plasma glucose: ≤140 mg/dl, >140 mg/dl. The third sentence of the third paragraph under Secondary Outcomes (page 2434) should have read "From the longitudinel linear model, e mean glycated hemoglobin level of less than 7% was maintained until the visit at 57 months in the rosiglitazone group" rather than "60 months." In Figure 4A (page 2436), the Treatment difference (95% CI) for rosiglitazone vs. metformin should have been −9.8 (−12.6 to −7.0). In Figure 4G (page 2437), the Annualized slope (95% CI) should have been −0.12 (−0.32 to 0.07) for metformin end 0.12 (−0.10 to 0.34) for glyburide. In Figure 4H (page 2437), the Annuelized slope (95% CI) should have been 0.0010 (−0.0006 to 0.0026) for metformin and 0.0011 (−0.0007 to 0.0029) for glyburide. In the Discussion section, the third sentence of the second paragraph (page 2439) should have read "By comparing three drugs head to head, our study provides long-term evidence that progressive loss of glycemic control can be delayed and a mean level of glycatad hemoglobin maintained at less than 7% for a longer period with rosiglitazone (57 months)" rather than "60 months." The second sentence of the fifth paragraph in the ssme section (page 2440) should have read "The protocol specified that all patients be free of known CHF on entry into the study. However, a retrospective review of source documents revealed that 17 patients (5 in the rosiglitazone group, 6 in the metformin group, and 6 in the glyburide group) entered the study with a current diagnosis of CHF. Only one of these patients (randomized to metformin) contributed to the events of CHF that are detailed in Table 2" rather than "At study entry, all patients were free of known CHF." The article has been corrected on the *Journal*'s Web site at www.nejm.org.

EXHIBIT 37

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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

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ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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THIAZOLIDINEDIONE DRUGS ARE WIDELY used to lower blood glucose levels in patients with type 2 diabetes mellitus. In the United States, three such agents have been introduced: troglitazone, which was removed from the market because of hepatotoxicity, and two currently available agents, rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda). The thiazolidinediones are agonists for peroxisome-proliferator–activated receptor γ (PPAR-γ). PPAR-γ receptors are ligand-activated nuclear transcription factors that modulate gene expression, lowering blood glucose primarily by increasing insulin sensitivity in peripheral tissues.[1,2] Rosiglitazone was introduced in 1999 and is widely used as monotherapy or in fixed-dose combinations with either metformin (Avandamet, GlaxoSmithKline) or glimepiride (Avandaryl, GlaxoSmithKline).

The original approval of rosiglitazone was based on the ability of the drug to reduce blood glucose and glycated hemoglobin levels.[3] Initial studies were not adequately powered to determine the effects of this agent on microvascular or macrovascular complications of diabetes, including cardiovascular morbidity and mortality.[3] However, the effect of any antidiabetic therapy on cardiovascular outcomes is particularly important, because more than 65% of deaths in patients with diabetes are from cardiovascular causes.[4] Therefore, we performed a meta-analysis of trials comparing rosiglitazone with placebo or active comparators to assess the effect of this agent on cardiovascular outcomes. The source material for this analysis consisted of publicly available data from the original registration package submitted to the Food and Drug Administration (FDA), another series of trials performed by the sponsor after approval, and two large, prospective, randomized trials designed to study additional indications for the drug.

METHODS

ANALYZED STUDIES

Table 1 lists the 42 trials included in this meta-analysis. We screened 116 phase 2, 3, and 4 trials for inclusion. Of these, 48 trials met the predefined inclusion criteria of having a randomized comparator group, a similar duration of treatment in all groups, and more than 24 weeks of drug exposure. Six of the 48 trials did nor report any myocardial infarctions or deaths from cardiovascular causes and therefore were not included in the analysis because the effect measure could not be calculated. Of the remaining 42 studies, 38 reported at least one myocardial infarction, and 23 reported at least one death from cardiovascular causes. In these trials, 15,565 patients were randomly assigned to regimens that included rosiglitazone, and 12,282 were assigned to comparator groups with regimens that did not include rosiglitazone.

Multiple groups of patients who received rosiglitazone within a single trial were pooled together, when applicable. The control group was defined as patients receiving any drug regimen other than rosiglitazone. The trials fall into three categories. One group includes five of the studies submitted to the FDA for the March 22, 1999, advisory board hearing that recommended approval of rosiglitazone. Group-level data from these five studies are available in publicly disclosed briefing documents archived on the FDA Web site.[6] Data from these same trials are also reported in a summary fashion on a clinical-trial registry Web site maintained by the drug manufacturer, GlaxoSmithKline.[5] Reports of four of these five trials were also published in peer-reviewed journals.[7-9] In these five trials, 1967 patients were randomly assigned to receive rosiglitazone, and 793 patients were assigned to receive various comparator drugs (Table 1).

Other studies that we included in the meta-analysis were initially identified in the GlaxoSmithKline clinical-trial registry.[5] As noted in Table 1, we included 35 studies in this category, 9 of which were published in peer-reviewed journals and 26 of which remain unpublished.[10-18] Whenever possible, the results obtained on the GlaxoSmithKline Web site were cross-checked with the publication. In cases of disagreement between published and unpublished data, data derived from the manufacturer's Web site were used. In this group of 35 trials, 9507 patients were randomly assigned to receive rosiglitazone, and 5960 patients were assigned to receive various comparator drugs.

A third data source consisted of two large, recently published trials, the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication (DREAM) NCT00095654 trial[20] and the A Diabetes Outcome Prevention Trial (ADOPT)

(ClinicalTrials.gov number, NCT00279045).[21] In the DREAM study, 2635 patients were randomly assigned to receive rosiglitazone and 2634 patients were assigned to receive placebo. The DREAM study was designed to determine whether rosiglitazone could prevent the development of type 2 diabetes in patients at high risk for this disorder. In the ADOPT trial, 1456 patients were randomly assigned to receive rosiglitazone and 2895 patients were assigned to receive either metformin or glyburide. The ADOPT study was designed to assess the durability of glycemic control with rosiglitazone therapy, as compared with therapy with metformin or glyburide.

OUTCOME MEASURES

We reviewed data summaries provided in the FDA review documents, the GlaxoSmithKline clinical-trial registry Web site, and published trial results and then abstracted from the adverse-event tabulations information on myocardial infarction and death from cardiovascular causes. With the exception of the DREAM study, the included trials did not describe adjudication of myocardial infarction or death from cardiovascular causes. Time-to-event data for cardiovascular events were not available in any of these trials, which precluded the calculation of hazard ratios. Because only summary data were available, it was not possible to discern whether the same patient had both events. Therefore, an outcome measure based on the composite of death or myocardial infarction could not be constructed. Accordingly, these two outcomes are reported separately.

STATISTICAL ANALYSIS

Many trials had few cardiovascular events, so the odds ratios and 95% confidence intervals were calculated with the use of the Peto method.[22-24] Because all trials had similar durations of follow-up for all treatment groups, the use of odds ratios represents a valid approach to assessing the risk associated with the use of rosiglitazone. Trials in which patients had no adverse cardiovascular events in either group were excluded from analyses. All reported P values are two-sided. Statistical heterogeneity across the various trials was tested with the use of Cochran's Q statistic. A P value of more than the nominal level of 0.10 for the Q statistic indicated a lack of heterogeneity across trials, allowing for the use of a fixed-effects model. For additional analyses, the active comparator control groups were subgrouped into the following four classes for comparison with rosiglitazone: metformin, sulfonylurea, insulin, and placebo. Odds ratios and 95% confidence intervals were calculated for each subgroup with the use of methods similar to those used in the pooled analyses. Data were analyzed with the use of Comprehensive Meta-Analysis software, version 2.2 (Biostat).

RESULTS

BASELINE CHARACTERISTICS

Table 2 reports the doses of rosiglitazone and comparator drugs, baseline demographic characteristics, study periods, and glycated hemoglobin levels or fasting blood glucose levels for patients enrolled in the trials. The patients were relatively young, averaging less than 57 years of age for both the rosiglitazone group and the control group. Overall, there was a moderate predominance of men. Diabetes control was relatively poor, with a mean baseline glycated hemoglobin level of approximately 8.2% for both study groups.

MYOCARDIAL INFARCTION AND DEATH

Table 3 reports the myocardial infarction events and deaths from cardiovascular causes that were reported in the 42 clinical trials we reviewed. There were 86 myocardial infarctions in the rosiglitazone group and 72 in the control group. There were 39 deaths from cardiovascular causes in the rosiglitazone group and 22 in the control group. Table 4 lists the odds ratios, 95% confidence intervals, and P values for myocardial infarction and death from cardiovascular causes for the rosiglitazone group and the control group. The summary odds ratio for myocardial infarction was 1.43 in the rosiglitazone group (95% confidence interval [CI], 1.03 to 1.98; P=0.03). The odds ratio for death from cardiovascular causes in the rosiglitazone group, as compared with the control group, was 1.64 (95% CI, 0.98 to 2.74; P=0.06). Table 4 also lists odds ratios and 95% confidence intervals for the pooled group of trials that were smaller and of shorter duration; results for the DREAM and ADOPT studies are shown separately.

Table 5 lists odds ratios for myocardial in-

Table 1. Clinical Trials of Rosiglitazone in the Meta-Analysis.[a]

Study and Reference	Registry Number	Phase	Duration	Rosiglitazone Group		Control Group	
			Drug	Drug	No. of Patients	Drug	No. of Patients
			wk				
Trials included in original registration package							
49653/011[5-7]		3	24	Rosiglitazone	357	Placebo	176
49653/020[5,8]		3	52	Rosiglitazone	391	Glyburide	207
49653/024[5,8,9]		3	26	Rosiglitazone	774	Placebo	185
49653/093[5,8,9]		3	26	Rosiglitazone with or without metformin	213	Metformin	109
49653/094[5,8,9,10]		3	26	Rosiglitazone and metformin	232	Metformin	116
Subtotal					1,967		793
Additional phase 2, 3, and 4 efficacy trials							
100684[5]		4	52	Rosiglitazone and glyburide	43	Glyburide	47
49653/143[5]		4	24	Rosiglitazone and glyburide	121	Glyburide	124
49653/211[5]		4	52	Rosiglitazone and usual care	110	Usual care	114
49653/284[5,11]		4	24	Rosiglitazone and metformin	382	Metformin	384
712753/008[5]		4	48	Rosiglitazone and metformin	284	Metformin	135
AVM100264[5]	NCT00359112	4	52	Rosiglitazone and metformin	294	Metformin and sulfonylurea†	302
BRL 49653C/185[5]		4	32	Rosiglitazone with or without metformin	563	Usual care with or without metformin	142
BRL 49653/334[5]		4	52	Rosiglitazone	278	Placebo	279
BRL 49653/347[5]	NCT00054782	4	24	Rosiglitazone and insulin	418	Insulin	212
49653/015[5,12]		3	24	Rosiglitazone and sulfonylurea‡	395	Sulfonylurea‡	198
49653/079[5]		3	26	Rosiglitazone with or without glyburide	203	Glyburide	106
49653/080[5,13]		3	156	Rosiglitazone	104	Glyburide	99
49653/082[5,14]		3	26	Rosiglitazone and insulin	212	Insulin	107
49653/085[5]		3	26	Rosiglitazone and insulin	138	Insulin	139
49653/095[5]		3	26	Rosiglitazone and insulin	196	Insulin	96
49653/097[5]		3	156	Rosiglitazone	122	Glyburide	120

49653/125[9,13]		3	26	Rosiglitazone and sulfonylurea§	175	Sulfonylurea§		173
49653/127[9]		3	26	Rosiglitazone and glyburide	56	Glyburide		58
49653/128[9]		3	28	Rosiglitazone	39	Placebo		38
49653/134[5]		3	28	Rosiglitazone	561	Placebo		276
49653/135[9]		3	104	Rosiglitazone and glipizide	116	Glipizide		111
49653/136[9]		3	26	Rosiglitazone	148	Placebo		143
49653/145[9,14]		3	26	Rosiglitazone and gliclazide	231	Gliclazide		242
49653/147[9,17]		3	26	Rosiglitazone and sufonylurea¶	89	Sulfonylurea¶		88
49653/162[9,14]		3	26	Rosiglitazone and glyburide	168	Glyburide		172
49653/234[5]		3	26	Rosiglitazone and glimepiride	116	Glimepiride		61
49653/330[5]		3	52	Rosiglitazone	1,181	Placebo		382
49653/331[5]		3	52	Rosiglitazone	706	Placebo		325
49653/137[5]		3	32	Rosiglitazone and metformin	204	Glyburide and metformin		185
SB-712753/002[5]		3	24	Rosiglitazone and metformin	288	Metformin		280
SB-712753/003[5]		3	32	Rosiglitazone and metformin	254	Metformin		272
SB-712753/007[5]		3	32	Rosiglitazone with or without metformin	314	Metformin		154
SB-712753/009[5]		3	24	Rosiglitazone, metformin, and insulin	162	Insulin		160
49653/132[9,15]		2	24	Rosiglitazone and sulfonylurea‖	442	Sulfonylurea‖		112
AVA100193[5]		2	24	Rosiglitazone	394	Placebo		124
Subtotal					9,507			5,960
Recently published large, prospective, randomized trials								
DREAM[20]	NCT00095654	3	156	Rosiglitazone	2,635	Placebo		2,634
ADOPT[21]	NCT00279045	3	208	Rosiglitazone	1,456	Metformin or glyburide		2,895
Total					15,565			12,282

* Studies are listed according to the number designated by the sponsor, GlaxoSmithKline, and are available on the company's Web site.[5] ClinicalTrials.gov numbers are listed for trials included in that registry. DREAM denotes Diabetes Reduction Assessment with Ramipiril and Rosiglitazone Medication, and ADOPT A Diabetes Outcome Prevention Trial.
† The administered drug was either glyburide or gliclazide.
‡ The administered drug was glyburide, gliclazide, or glipizide.
§ The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, glimepiride, or tolbutamide.
¶ The type of sulfonylurea was unspecified.
‖ The administered drug was glyburide, glipizide, gliclazide, chlorpropamide, gliquidone, or tolbutamide.

Table 2. Doses, Baseline Demographic Characteristics, Study Periods, and Glycated Hemoglobin Levels.*

Study	Drug	Daily Dose	Population	Study Period	Age	Male Sex	Race†	Baseline Glycated Hemoglobin Level
					yr		*percent*	
100684	Rsg/Gly	4 or 8 mg	Korean patients with type 2 DM	Dec. 2003–July 2005	55.2	53.5	100 A	NA
	Gly	5–15 mg			54.5	45.6	100 A	NA
49653/143	Rsg/Gly	8 mg	Type 2 DM poorly controlled on glyburide	July 2000–Jan. 2003	52	45.3	44:56 B:H	9.2
	Gly	Usual care			53	48.3	38:62 B:H	9.4
49653/211	Rsg	4 mg	Type 2 DM with CHF	July 2001–Nov. 2003	64.3	84.3	99	7.7
	Plc	—			63.9	79.0	99	7.8
49653/284	Rsg/Met	4 or 8 mg/1 g	Type 2 DM	June 2001–Feb. 2003	55.5	51.1	72	8.1
	Met	1–2 g			55.6	51.0	71	7.9
712753/008	Rsg/Met	8 mg/1 g	Type 2 DM poorly controlled on Met	June 2003–Dec. 2005	54.6	63.2	70	NA
	Rsg/Met	4 mg/2 g			56.0	65.2	78	NA
	Met	2g			56.9	53.4	69	NA
AVM100264	Rsg/Met	4 or 8 mg/2 g	Overweight patients with type 2 DM poorly controlled on Met	July 2004–Jan. 2006	58.5	52.7	94	8.0
	Met/Su	2 g/titrated			59.3	52.5	95	8.0
BRL49653C/185	Rsg/ELM/Met	4 mg/1.5 g	Type 2 DM	May 2000–May 2002	58.0	65.2	76	7.5
	Rsg/ELM	4 mg			59.0	60.2	78	7.4
	Met/ELM	1.5 g			60.0	56.4	78	7.5
	ELM	—			57.0	60.9	83	7.4
BRL 49653/334	Rsg	4 or 8 mg	Type 2 DM or insulin resistance syndrome	March 2002–Nov. 2004	67.7	44.8	99	6.3
	Plc	—			67.3	47.7	100	6.3
BRL 49653/347	Rsg/insulin	4 mg	Type 2 DM poorly controlled on insulin	Nov. 2002–April 2004	52.6	48.1	57	9.0
	Rsg/insulin	2 or 4 mg			52.7	60.0	57	8.9
	Insulin/Plc	Usual care			53.8	46.2	57	9.1
49653/011	Rsg	8 mg	Type 2 DM	Sept. 1996–Sept. 1997	60.7	66.9	73	8.8
	Rsg	4 mg			59.6	64.5	75	9.0
	Plc	—			58.8	65.8	74	9.0
49653/015	Rsg/Su	4 mg	Type 2 DM	Aug. 1996–March 1998	60.6	53.2	98	9.2
	Rsg/Su	2 mg			61.0	62.8	86	9.2
	Su				61.9	57.3	97	9.2

49653/020	Rsg	8 mg	Type 2 DM	Oct. 1996–May 1998	60.9	57.6	97		8.2
	Rsg	4 mg			60.4	68.2	99		8.1
	Gly	Titrated			60.1	70.4	99		8.2
49653/024	Rsg	4 mg once daily	Type 2 DM	Jan. 1997–Feb. 1998	57.5	58.6	76		8.9
	Rsg	2 mg twice daily			56.8	59.1	78		8.9
	Rsg	8 mg once daily			58.9	65.7	80		8.9
	Rsg	4 mg twice daily			56.5	59.9	71		9.0
	Plc	—			57.7	68.8	79		8.9
49653/079	Rsg	4 mg	Type 2 DM poorly controlled on maximum dose of Gly	April 1997–March 1998	59.1	63.6	70		9.1
	Rsg/Gly	4 mg/20 mg			57.7	69.4	70		9.2
	Gly	20 mg			58.5	66.7	69		9.3
49653/080	Rsg	8 mg	Type 2 DM	Nov. 1996–May 2000	55.1	75.0	73		8.9
	Gly	2.5–5.0 mg			56.1	70.1	76		9.4
49653/082	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	July 1997–Aug. 1998	57.7	54.3	71		9.0
	Rsg/insulin	4 mg			57.1	56.6	72		9.1
	Insulin	Usual care			55.6	55.8	68		8.9
49653/085	Rsg/insulin	4 or 8 mg	Type 2 DM	May 2000–June 2001	61.3	54.0	99		NA
	Insulin	Usual care			61.5	46.8	100		NA
49653/093	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled on Met	June 1997–April 1998	57.8	60.0	58		8.7
	Rsg	8 mg			58.8	53.7	59		8.7
	Met	2.5 g			59.5	67.0	60		8.8
49653/094	Rsg/Met	8 mg/2.5 g	Type 2 DM poorly controlled on Met	April 1997–March 1998	58.3	68.2	77		8.9
	Rsg/Met	4 mg/2.5 g			57.5	62.1	80		8.9
	Met	2.5 g			58.8	74.3	81		8.6
49653/095	Rsg/insulin	8 mg	Type 2 DM poorly controlled on insulin	Aug. 1997–Dec. 1998	57.4	58.9	73		9.1
	Rsg/insulin	4 mg			57.8	63.9	68		8.8
	Insulin	Usual care			58.9	45.3	73		9.1
49653/097	Rsg	8 mg	Type 2 DM	Aug. 1997–Jan. 2001	55.8	72.1	74		8.9
	Gly	Titrated			56.0	70.8	84		8.8
49653/125	Rsg/Su	4 mg	Type 2 DM	May 1999–Aug. 2000	54.6	45.7	56	A	9.1
	Su	Usual care			57.3	42.4	59	A	8.9
49653/127	Rsg/Gly	8 mg/<20 mg	Type 2 DM poorly controlled on Gly	Jan. 1999–Dec. 1999	60.0	51.0	75		9.1
	Gly	<20 mg			59.4	66.0	75		8.9

Table 2. (Continued.)

Study	Drug	Dose	Population	Study Period	Age	Male Sex	Race†	Baseline Glycated Hemoglobin Level
					yr		*percent*	
49653/128	Rsg/Su	4 mg	Type 2 DM on concurrent Su	May 1999–June 2000	58.3	51.3	100 A	9.6
	Su	Usual care			57.7	42.1	100 A	9.9
49653/134	Rsg/Gly/Met	8 mg	Type 2 DM on Gly and Met	March 1999–Aug. 2000	55.5	62.0	71	8.7
	Rsg/Gly/Met	4 mg			55.6	58.0	68	8.6
	Gly/Met	Usual care			55.8	61.0	71	8.7
49653/135	Rsg/Glip	4 or 8 mg/ 20–40 mg	Elderly patients with type 2 DM	May 1999–Oct. 2002	68.7	74.1	90	7.6
	Glip	20–40 mg			68.2	71.2	91	7.3
49653/136	Rsg/Su/insulin	4 or 8 mg	Type 2 DM with chronic renal failure on Su, insulin, or both	July 1999–June 2001	64.9	60.7	97	8.2
	Su/insulin	Usual care			66.3	60.8	98	8.3
49653/145	Rsg/Su	8 mg	Type 2 DM	Oct. 1999–Nov. 2000	61.1	57.3	97	8.5
	Su	Usual care			61.9	62.7	98	8.6
49653/147	Rsg/Su	8 mg	Indo-Asian patients with type 2 DM	July 1999–Aug. 2000	54.3	20.2	100 A	9.2
	Su	Usual care			54.1	25.3	100 A	9.1
49653/162	Rsg/Gly	8 mg	Type 2 DM	Nov. 2000–April 2002	60.0	55.1	97	7.9
	Gly	Maximum, 15 mg			59.9	61.8	96	8.0
49653/234	Rsg/Glim	8 mg	Type 2 DM	Jan. 2001–Feb. 2002	62.9	44.0	100	8.1
	Rsg/Glim	4 mg			60.5	57.0	100	8.2
	Glim	Up-titrated			65.0	60.0	100	7.9
49653/330	Rsg	8 mg	Chronic psoriasis	Jan. 2003–Oct. 2004	44.3	65.0	92	NA
	Rsg	4 mg			44.8	66.0	91	NA
	Rsg	2 mg			45.0	63.0	90	NA
	Plc	—			44.5	63.0	93	NA
SB-712753/003	Rsg/Met	4 or 8 mg/1–3 g	Mild type 2 DM	June 2003–Dec. 2004	58.9	54.7	98	7.2
	Met	1–3 g			59.0	55.5	99	7.2

49653/331	Rsg	4 mg	Chronic psoriasis	Jan. 2003–Oct. 2004	44.9	64.1	88	NA		
	Rsg	2 mg			45.2	62.0	90	NA		
	Plc	—			46.4	58.3	93	NA		
49653/137	Rsg/Met	≥2 mg/≥1 g	Type 2 DM	April 2000–March 2004	60.0	63.4	78	NA		
	Gly/Met	≥5 mg/≥1 g			58.8	68.9	76			
SB-712753/002	Rsg/Met	4 or 8 mg/2–3 g	Type 2 DM poorly controlled	July 2003–June 2004	58.1	58.3	97	7.4		
	Met	2–3 g			57.6	56.8	98	7.5		
SB-712753/007	Rsg/Met	2 or 8 mg/0.5-2.0 g	Type 2 DM without previous drug therapy	Oct. 2003–Dec. 2004	50.1	57.4	54	8.9		
	Rsg	4 or 8 mg			51.5	56.5	58	8.8		
	Met	0.5–2.0 g			50.6	58.5	59	8.8		
SB-712753/009	Rsg/Met/Insulin	8 mg/2 g	Type 2 DM with insulin	Oct. 2003–Nov. 2004	57.2	51.8	98	8.7		
	Insulin	Usual care			56.9	53.1	99	8.8		
49653/132	Rsg/Su	4 mg/usual care	Patients in China with type 2 DM	April 1999–Feb. 2000	58.9	47.6	100 A	9.9		
	Rsg/Su	8 mg/usual care			59.0	41.4	100 A	9.7		
	Su	Usual care			58.8	45.7	100 A	9.6		
AVA100193	Rsg	2 mg	Mild-to-moderate Alzheimer's disease	Jan. 2004–May 2005	71.0	44.1	100	NA		
	Rsg	4 mg			70.0	43.8	100	NA		
	Rsg	8 mg			71.0	34.1	100	NA		
	Plc	—			72.0	36.9	100	NA		
DREAM	Rsg	4 or 8 mg	Impaired glucose tolerance or fasting glucose	July 2001–Aug. 2003	54.6	41.7	66	104.5‡		
	Plc	—			54.8	39.9	66	104.5‡		
ADOPT	Rsg	4 mg	Recently diagnosed type 2 DM	April 2000–June 2002	56.3	55.7	87	7.4		
	Met	500 mg			57.9	59.4	89	7.4		
	Gly	2.5 mg			56.4	58.0	89	7.4		
Weighted adjusted means§										
	Rsg				56.1	60.7	84.4	8.2		
	Control				56.9	53.3	77.5	8.2		

* Rsg denotes rosiglitazone, DM diabetes mellitus, Gly glyburide, Plc placebo, CHF congestive heart failure, Met metformin, ELM enhanced lifestyle management, Su sulfonylurea, Glip glipizide, Glim glimepiride, and NA not available.
† Percentages are the proportion of white patients, unless otherwise specified as black (B), Hispanic (H), or Asian (A).
‡ The fasting plasma glucose level (in milligrams per deciliter) is listed.
§ Weighted adjusted means were calculated for the rosiglitazone and control groups by multiplying individual means by sample sizes, adding them together, and dividing the sum by the total sample size for each treatment group.

Table 3. Myocardial Infarctions and Cardiovascular Deaths in Rosiglitazone Trials.

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		number			*number*	
49653/011	357	2	1	176	0	0
49653/020	391	2	0	207	1	0
49653/024	774	1	0	185	1	0
49653/093	213	0	0	109	1	0
49653/094	232	1	1	116	0	0
100684	43	0	0	47	1	0
49653/143	121	1	0	124	0	0
49653/211	110	5	3	114	2	2
49653/284	382	1	0	384	0	0
712753/008	284	1	0	135	0	0
AVM100264	294	0	2	302	1	1
BRL 49653C/185	563	2	0	142	0	0
BRL 49653/334	278	2	0	279	1	1
BRL 49653/347	418	2	0	212	0	0
49653/015	395	2	2	198	1	0
49653/079	203	1	1	106	1	1
49653/080	104	1	0	99	2	0
49653/082	212	2	1	107	0	0
49653/085	138	3	1	139	1	0
49653/095	196	0	1	96	0	0
49653/097	122	0	0	120	1	0
49653/125	175	0	0	173	1	0
49653/127	56	1	0	58	0	0
49653/128	39	1	0	38	0	0
49653/134	561	0	1	276	2	0
49653/135	116	2	2	111	3	1
49653/136	148	1	2	143	0	0
49653/145	231	1	1	242	0	0
49653/147	89	1	0	88	0	0
49653/162	168	1	1	172	0	0
49653/234	116	0	0	61	0	0
49653/330	1172	1	1	377	0	0
49653/331	706	0	1	325	0	0
49653/137	204	1	0	185	2	1
SB-712753/002	288	1	1	280	0	0
SB-712753/003	254	1	0	272	0	0
SB-712753/007	314	1	0	154	0	0
SB-712753/009	162	0	0	160	0	0
49653/132	442	1	1	112	0	0

Table 3. (Continued.)

Study	Rosiglitazone Group			Control Group		
	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause	No. of Patients	Myocardial Infarction	Death from Cardiovascular Cause
		number			*number*	
AVA100193	394	1	1	124	0	0
DREAM	2635	15	12	2634	9	10
ADOPT	1456	27	2	2895	41	5
Total		86	39		72	22

farction and death from cardiovascular causes associated with rosiglitazone for subgroups defined according to the comparator drug. Similar results were obtained when the analysis excluded trials with an active comparator group. The heterogeneity P values were 0.53 for myocardial infarction and 0.68 for death from cardiovascular causes across subgroups. As compared with placebo or other antidiabetic regimens, the estimated odds ratios in all cases were greater than 1.0, suggesting that observed adverse effects during rosiglitazone treatment were not unique to any specific comparator regimen.

In an analysis that was not prespecified, we also studied the effects of rosiglitazone on death from any cause. The odds ratio for death from any cause was 1.18 (95% CI, 0.89 to 1.55; P=0.24).

DISCUSSION

Our data show that, as compared with placebo or with other antidiabetic regimens, treatment with rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that was of borderline significance. The similar odds ratio for comparison with placebo suggests that the increased risk associated with rosiglitazone was not a function of the protective effects of active comparator drugs. However, these findings are based on limited access to trial results from publicly available sources, not on patient-level source data. Furthermore, results are based on a relatively small number of events, resulting in odds ratios that could be affected by small changes in the classification of events. Nonetheless, our findings are worrisome because of the high incidence of cardiovascular events in patients with diabetes.[4] Because exposure of such patients to rosiglitazone is widespread, the public health impact of an increase in cardiovascular risk could be substantial if our data are borne out by further analysis and the results of larger controlled trials.

Although we did not have access to the source data to construct a composite outcome that included myocardial infarction or death from cardiovascular causes, the increase in the odds ratios for both of these end points suggests that observed adverse effects associated with rosiglitazone were probably not due to chance alone. This meta-analysis included a group of trials that were of relatively short duration (24 to 52 weeks). The odds ratio for these shorter-term trials was similar to the overall results of the meta-analysis. Thus, in susceptible patients, rosiglitazone therapy may be capable of provoking myocardial infarction or death from cardiovascular causes after relatively short-term exposure. In contrast, long-term therapies that improve cardiovascular outcomes, such as statins and antihypertensive drugs, often take several years to provide benefits. Notably, the estimates for the odds ratios for myocardial infarction and death from cardiovascular causes appear elevated for rosiglitazone in comparison with placebo or other commonly prescribed antidiabetic therapies (Table 5).

The mechanism for the apparent increase in myocardial infarction and death from cardiovascular causes associated with rosiglitazone remains uncertain. One potential contributing factor may be the adverse effect of the drug on serum lipids. The FDA-approved rosiglitazone product label reports a mean increase in low-density lipoprotein (LDL) cholesterol of 18.6% among patients treated for 26 weeks with an 8-mg daily dose, as compared with placebo.[25] In observational studies and lipid-lowering trials, elevated levels of

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

LDL cholesterol were associated with an increase in adverse cardiovascular outcomes. Thus, an increase in LDL cholesterol of the magnitude observed in the rosiglitazone group may have contributed to adverse cardiovascular outcomes, although the rapidity and magnitude of the apparent hazard was not consistent with an effect produced by lipid changes alone.

Several other properties of rosiglitazone may contribute to adverse cardiovascular outcomes. Rosiglitazone and other thiazolidinediones are known to precipitate congestive heart failure in susceptible patients.[26] Congestive heart failure is a physiological state that is associated with an increased intravascular volume. Volume overload increases stress on the left ventricular wall, a factor that determines myocardial oxygen demand. In susceptible patients, an increase in myocardial oxygen demand could theoretically provoke ischemic events. The administration of thiazolidinediones, including rosiglitazone, also produces a modest reduction in the hemoglobin level.[25] In susceptible patients, a reduced hemoglobin level may result in increased physiological stress, thereby provoking myocardial ischemia. A study of rosiglitazone that was conducted in rats reported an increase in the rate of death after experimentally induced myocardial infarction.[27]

Rosiglitazone is not the first PPAR agonist that has been reported to increase adverse cardiovascular events. Muraglitazar, an investigational dual PPAR-α and PPAR-γ agonist, increased adverse cardiovascular events, including myocardial infarction, during phase 2 and 3 testing.[28] After publication of an analysis of cardiovascular outcomes, muraglitazar was not approved by the FDA, and further development was subsequently halted by the manufacturer. Development programs for many other PPAR agonists have been terminated after evidence of toxicity emerged during preclinical studies or initial trials in humans. According to a former FDA official, more than 50 Investigational New Drug applications for novel PPARs have been filed, but no additional drugs have successfully reached the market in more than 6 years.[29] In some cases, these drugs have failed because of evidence of direct myocardial toxicity in studies in animals,[29] but few data on toxicity are available in the public domain because of the common industry practice of not publishing safety findings for failed products.

PPAR agonists such as rosiglitazone have very complex biologic effects, resulting from the activation or suppression of dozens of genes.[30] The patterns of gene activation or suppression differ substantially among various PPAR agonists, even within closely related compounds. The biologic effects of the protein targets for most of the genes influenced by PPAR agonists remain largely unknown. Accordingly, many different and seemingly unrelated toxic effects have emerged during development of other PPAR agents.[29] Some drugs have provoked multispecies, multiorgan system cancers; others have resulted in rhabdomyolysis or nephrotoxicity.[29] Troglitazone was withdrawn from the market for rare, but

sometimes fatal, liver toxicity. Accordingly, it must be assumed that a variety of unexpected toxic effects are possible when PPAR agonists are administered to patients.

The question as to whether the observed risks of rosiglitazone represent a "class effect" of thiazolidinediones must also be considered. Pioglitazone is a related agent also widely used to treat type 2 diabetes mellitus. However, unlike rosiglitazone, pioglitazone has been studied in a prospective, randomized trial of cardiovascular outcomes, called Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE).[31] The primary end point, a broad composite that included coronary and peripheral vascular events, showed a trend toward benefit from pioglitazone (hazard ratio, 0.90; P=0.095). A secondary end point consisting of myocardial infarction, stroke, and death from any cause showed a significant effect favoring pioglitazone (hazard ratio, 0.84; P=0.027). Notably, pioglitazone appears to have more favorable effects on lipids, particularly triglycerides, than does rosiglitazone.[32]

These emerging findings raise an important question about the appropriateness of the current regulatory pathways for the development of drugs to treat diabetes. The FDA considers demonstration of a sustained reduction in blood glucose levels with an acceptable safety profile adequate for approval of antidiabetic agents. However, the ultimate value of antidiabetic therapy is the reduction of the complications of diabetes, not improvement in a laboratory measure of glycemic control. Although reductions in blood glucose levels have been shown to reliably reduce microvascular complications of diabetes, the effect on macrovascular complications has proved to be unpredictable.[33] After the failure of muraglitazar and the apparent increase in adverse cardiovascular outcomes with rosiglitazone, the use of blood glucose measurements as a surrogate end point in regulatory approval must be carefully reexamined.

Our study has important limitations. We pooled the results of a group of trials that were not originally intended to explore cardiovascular outcomes. Most trials did not centrally adjudicate cardiovascular outcomes, and the definitions of myocardial infarction were not available. Many of these trials were small and short-term, resulting in few adverse cardiovascular events or deaths. Accordingly, the confidence intervals for the odds ratios for myocardial infarction and death from cardiovascular causes are wide, resulting in considerable uncertainty about the magnitude of the observed hazard. Furthermore, we did not have access to original source data for any of these trials. Thus, we based the analysis on available data from publicly disclosed summaries of events. The lack of availability of source data did not allow the use of more statistically powerful time-to-event analysis. A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest. Although such a dedicated trial has not been completed for rosiglitazone, the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial may provide useful insights.[34]

Despite these limitations, our data point to the urgent need for comprehensive evaluations to clarify the cardiovascular risks of rosiglitazone. The manufacturer's public disclosure of summary results for rosiglitazone clinical trials is not sufficient to enable a robust assessment of cardiovascular risks. The manufacturer has all the source data for completed clinical trials and should make these data available to an external academic coordinating center for systematic analysis. The FDA also has access to study reports

Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06

and other clinical-trial data not within the public domain. Further analyses of data available to the FDA and the manufacturer would enable a more robust assessment of the risks of this drug. Our data suggest a cardiovascular risk associated with the use of rosiglitazone. Until more precise estimates of the cardiovascular risk of this treatment can be delineated in patients with diabetes, patients and providers should carefully consider the potential risks of rosiglitazone in the treatment of type 2 diabetes.

Dr. Nissen reports receiving research support to perform clinical trials through the Cleveland Clinic Cardiovascular Coordinating Center from Pfizer, AstraZeneca, Daiichi Sankyo, Roche, Takeda, Sanofi-Aventis, and Eli Lilly. Dr. Nissen consults for many pharmaceutical companies but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction. No other potential conflict of interest relevant to this article was reported.

We thank Craig Balog for statistical programming support.

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EXHIBIT 38

FOCUS - 11 of 15 DOCUMENTS

THE WALL STREET JOURNAL.
The Wall Street Journal

May 22, 2007 Tuesday

SECTION: Pg. A1

LENGTH: 2244 words

HEADLINE: Medical Detective -- Sequel for Vioxx Critic: Attack on Diabetes Pill --- Glaxo Shares Plunge As Dr. Nissen Sees Risk To Heart From Avandia

BYLINE: By Anna Wilde Mathews

BODY:

An analysis linking the widely used diabetes drug Avandia to higher risk of heart attacks represents a serious blow to GlaxoSmithKline PLC and underscores how outside critics have been empowered to challenge big-selling drugs after the outcry over the withdrawn painkiller Vioxx.

Glaxo rang up more than $3 billion in world-wide sales of Avandia last year. Its share price fell more than 7% after the New England Journal of Medicine released the analysis by prominent cardiologist Steven Nissen of the Cleveland Clinic, who helped raise early safety concerns about Vioxx. The analysis suggested that people on Avandia have a 43% higher chance of suffering a heart attack.

Glaxo said it "strongly disagrees" with his conclusions, which come from a "meta-analysis" in which results from many trials are combined. Glaxo said data sources it considers more reliable suggest that Avandia is no riskier for the heart than other diabetes medications.

Dr. Nissen started his quest to gather data about Avandia's risks last year, after he spotted what he thought were hints of trouble in published studies. Along the way, he set congressional investigations into motion, and, last month, hit pay dirt with a Google search that pointed him to a trove of study data. Brushing aside the arguments of Glaxo executives who rushed to Cleveland, he pushed his concerns into one of the world's top medical journals in just a few weeks.

One issue coming under congressional scrutiny is whether the Food and Drug Administration should have acted faster to alert the public about possible risk from Avandia. Glaxo performed its own meta-analysis, which also showed a potential danger. It shared an early version of it with the FDA in September 2005 and a more complete one in August 2006. The findings weren't reflected on the U.S. label, which is supposed to give a comprehensive review of the drug's risks.

Robert Meyer, head of the FDA office that oversees diabetes drugs, said the agency is still working on its analysis. "We have other data that suggests we can't make a definitive conclusion at this point," said Dr. Meyer, although he called the meta-analyses "a signal of concern."

The news sent doctors and patients taking Avandia scurrying to re-evaluate their options. Alternatives include a similar drug, Actos, made by Takeda Pharmaceutical Co., which didn't show a link to heart attacks or strokes in a trial published in the Lancet in 2005. Diabetes treatments that work in different ways, such as Merck & Co.'s Januvia, and older drugs like metformin could also gain sales.

"Cardiovascular disease is far and away the leading cause of death in diabetes. If you find a diabetes drug increases the risk of heart attacks, the consequences are so grave that it warrants urgent action," said Dr. Nissen, the 58-year-old chairman of cardiovascular medicine at the Cleveland Clinic, in an interview.

Dr. Nissen has consulted for drug companies including Glaxo. He is leading a small clinical trial of Actos funded by Takeda. He gives his drug-industry payments to charity and said his work for Takeda doesn't affect his view of competing drugs.

Cindy Roth, a diabetes patient in Whitewater, Kan., said the news about Avandia is a "little bit of a scare," in particular because heart problems run in her family. "I thought, 'Great, just one more thing,'" she said. Ms. Roth said she would follow her doctor's advice on whether to stop taking the drug.

Outside specialists are in a more powerful position these days to challenge marketed drugs. After the 2004 withdrawal of Merck's arthritis drug Vioxx and other well-publicized safety issues, the FDA is under pressure to respond more aggressively to signals of possible danger.

Prodded by lawmakers and medical journals, companies have put large databases of once-secret information about clinical trials online. The FDA's Web site also contains significant data on approved drugs. Dr. Nissen's Googling turned up a public database that GlaxoSmithKline created after it was sued over its antidepressant Paxil. The company had been accused of burying information about Paxil, including possible links to suicidal thinking in adolescents.

Dr. Nissen's analysis of Avandia combined 42 studies. In addition to showing higher heart-attack risk, it showed a 64% elevated risk of death from cardiovascular causes such as heart attack and stroke, although the latter result didn't meet a standard statistical test for significance.

The absolute risk of heart attacks and death was still low. Among people in Dr. Nissen's analysis who took Avandia, the rate of heart attack was between 0.43% and 1.85%, while the cardiovascular-death rate was between 0.14% and 0.51%.

About seven million people world-wide have taken Avandia, and about one million Americans are currently using it, GlaxoSmithKline said. Avandia is the London-based company's second-biggest seller after the asthma medication Advair, and last year various forms of the drug represented 37% of the U.S. market for oral diabetes treatments, according to the company. Glaxo has been studying Avandia as a possible treatment for people with early signs of diabetes and Alzheimer's patients.

Democratic Rep. Henry Waxman of California said he will hold a hearing in early June and summon FDA Commissioner Andrew von Eschenbach, Glaxo Chief Executive Jean-Pierre Garnier and Dr. Nissen.

A sharply worded editorial in the New England Journal of Medicine accompanying Dr. Nissen's study said "regulatory action by the Food and Drug Administration is now warranted." The editorial questioned the measure of effectiveness the FDA typically uses to approve diabetes drugs. The agency mostly examines how well the drugs reduce blood sugar, which is supposed to be a surrogate for improving more important outcomes, like heart disease. The FDA said yesterday it has strong evidence to suggest that reducing blood sugar translates into real-world benefit for patients.

Diabetes specialists were divided yesterday over whether patients taking Avandia should stop. "Patients and physicians need to take this seriously, in the absence of other data," said David Nathan, a professor at Harvard University. While calling the Nissen analysis "imperfectly done," he said: "Since heart disease is the major killer of people with diabetes, it's hard to imagine why you would use a drug that might increase the risk of heart disease."

John Buse, president-elect of the American Diabetes Association and a professor at the University of North Carolina, said he's "not sure the data are strong enough to encourage wholesale switching" from Avandia. "I doubt [Avandia] would be associated with a 40% increase in risk when the studies are done," he said.

Dr. Nissen has long been one of the nation's most prominent cardiologists. In the past few years, he has increasingly focused on drug safety. He was co-author of a 2001 analysis that flagged a possible heart risk with Vioxx and a similar painkiller, Celebrex. Merck initially dismissed the concerns, but pulled Vioxx three years later when its own study confirmed the risk.

In 2005, Dr. Nissen published an article in the Journal of the American Medical Association raising concerns about the cardiovascular risks associated with Pargluva, a diabetes drug that an FDA advisory panel had voted in favor of. The FDA declined to approve the drug and the companies hoping to market it, Merck and Bristol-Myers Squibb Co., abandoned the effort.

Dr. Nissen said that after his article about Pargluva appeared, he received an email from a leading diabetes expert who suggested that Avandia raised similar concerns.

Although their mode of action isn't identical, both Pargluva and Avandia work by affecting what are known as peroxisome proliferator-activated receptors, or PPARs. These are receptors in a cell's nucleus that affect a broad range of human genes. Because of their wide effect, many experimental PPAR drugs have been derailed by safety problems including possible hazards to the heart, kidney and muscles as well as tumors in animals.

Nonetheless, more than 50 PPAR drugs are being studied by pharmaceutical companies because the potential benefits are big too, according Pharmaprojects, a unit of Informa Healthcare Ltd. In Type 2 diabetes, patients don't produce enough insulin, a hormone needed to convert sugar and other food into energy, or their cells ignore the insulin that is being produced. Avandia and Actos, another PPAR drug, increase the sensitivity of cells to insulin, lowering blood sugar.

After their introduction in 1999, Avandia and Actos both soon became multibillion-dollar-a-year sellers. The labels on the two drugs have warned that they can cause fluid retention leading to congestive heart failure, a chronic condition in which the heart has trouble pumping blood. But regulators generally saw that as a manageable side effect. Signs of heart failure can be spotted early and treated with drugs, whereas in a heart attack, blood is choked off from the heart and immediate death can result.

Dr. Nissen said that even before the 2005 email, he had favored Actos. He had been nervous about Avandia because its label shows it is tied to an increase in LDL, or "bad" cholesterol, though company salespeople reassured him that HDL or "good" cholesterol also rose.

Dr. Nissen began following Avandia closely and was struck last year by the results of two major trials of the drug, published in the New England Journal of Medicine and the Lancet. The two studies showed the drug was effective in controlling blood sugar, but Dr. Nissen thought they held signs of cardiovascular problems.

He asked Kathy Wolski, a Cleveland Clinic statistician, to do a rough analysis combining studies published about the drug. The numbers, when added together, hinted at problems but didn't prove anything. "I honestly thought we weren't going to go any further with it," Ms. Wolski said. "He did not let it go. He was like a dog with a bone."

Dr. Nissen wrote to GlaxoSmithKline in early January, asking for more data. The company offered to collaborate

with him, but said it wanted to crunch the numbers itself. Dr. Nissen countered that the Cleveland Clinic needed full access to all the raw information and the right to publish as it pleased. Talks over the matter were inconclusive.

The cardiologist also shared his early results with congressional staffers, hoping they would use their authority to get the FDA to share trial results filed by the company. Aides to Democratic Rep. John Dingell of Michigan and Mr. Waxman called FDA officials in on March 16 to discuss their handling of Avandia.

In the end, it turned out humble Internet searches were all Dr. Nissen needed. In mid-April, he found online the 1999 FDA document detailing the agency's original review of the drug. Then, in a Google search, Dr. Nissen found the online database of Glaxo study results. Many of the trial summaries included heart-attack data.

Dr. Nissen made another discovery in scrolling through the Web site. The company itself had done a meta-analysis similar to the one he was attempting, and quietly posted the result. The analysis, which didn't appear to include the two big trials published last year, tied the drug to a 31% higher risk of events involving an obstruction of blood flow, such as heart attacks. The rate for people taking Avandia was 1.99%, compared with 1.51% for other patients.

Glaxo's summary said that "no definitive conclusion can be drawn." It noted that a separate study using a large database kept by a health insurer hadn't shown evidence of risk. "We are confident about the safety profile of Avandia," said Ronald Krall, Glaxo's chief medical officer, yesterday. Glaxo said ongoing trials haven't shown signs of a risk.

The Web site was a "gold mine," Dr. Nissen said. On May 1, he and Ms. Wolski sent the New England Journal of Medicine a manuscript tying Avandia to a statistically significant heart risk.

Glaxo learned of the submission and dispatched four executives to Cleveland. Dr. Krall argued that the data didn't clearly show a risk. Glaxo said yesterday that the meta-analysis technique isn't the most rigorous way to reach conclusions about safety issues because it combines studies that are designed differently and the data collected in the studies may not be comparable.

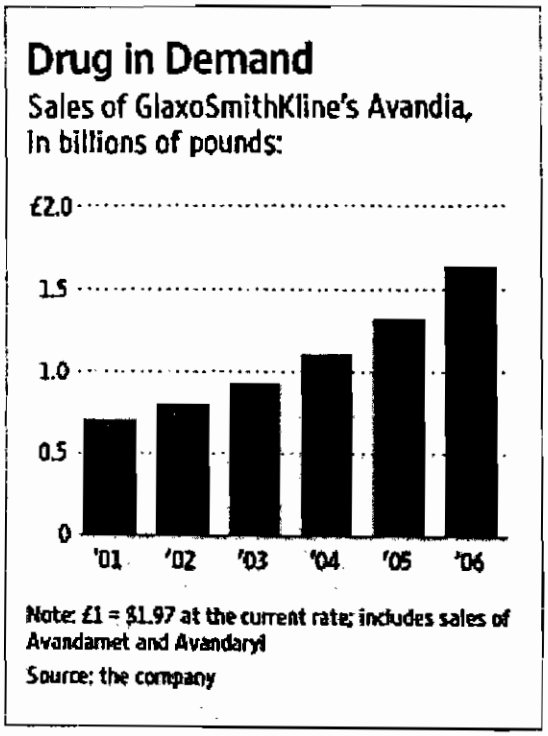
Dr. Nissen said the meeting was "very collegial and respectful," but the Glaxo team didn't change his mind about the safety concerns.

The New England Journal sharply accelerated its usual review process. "We felt it was our responsibility not to take eight, nine, 10 weeks to get this out," said Jeffrey Drazen, editor in chief.

With the data now public, the battle may shift to Capitol Hill. In a letter to the FDA dated April 30, the House Democrats plus Republican Sen. Charles Grassley expressed concern that "tens of thousands of excess heart attacks may have occurred" since the FDA began reviewing data from Glaxo's internal meta-analysis.

Yesterday, the Senate Finance Committee chairman, Montana Democrat Max Baucus, and Sen. Grassley sent a letter to Glaxo mentioning "reports that GSK employees silenced one or more medical professionals who attempted to speak out about the potential for cardiovascular problems with Avandia." In a statement, the company called the suggestion "absolutely false."

Jeanne Whalen and Sarah Rubenstein contributed to this article.



Steve Nissen

NOTES:
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LOAD-DATE: May 23, 2007

EXHIBIT 39

WSJ.com THE WALL STREET JOURNAL. ONLINE

May 23, 2007

In Europe, Warning on Avandia Is Old News

Glaxo Drug's Risks For Cardiac Events Were Cited Last Fall

By JEANNE WHALEN
May 23, 2007

Concerns about the safety of **GlaxoSmithKline** PLC's diabetes drug Avandia underscore the different approaches to medical regulation in different markets.

A day after U.S. politicians called on the U.S. Food and Drug Administration to strengthen its warnings on the drug, Europe's main medical regulator reiterated that it had strengthened warnings about Avandia's cardiovascular risks last fall based on company data available to regulators on both sides of the Atlantic.

Avandia came under fire Monday after a prominent U.S. cardiologist published a study in the New England Journal of Medicine linking the drug to possible heart-attack risks. The U.S. Food and Drug Administration is still deciding whether to change its guidance on the drug.

Physician and patient concerns about the drug's safety could cut Avandia's future sales in half, creating a big revenue hole for the British drug maker, analysts warned.

Morgan Stanley analyst Andrew Baum estimated that Avandia's sales by 2010 would be £1.2 billion ($2.36 billion), half of the £2.4 billion he had forecast before Avandia's safety was questioned by Steve Nissen, a cardiologist with the Cleveland Clinic. After reviewing dozens of clinical trials, Dr. Nissen concluded that patients who took Avandia had a 43% higher chance of suffering a heart attack than those who took other oral diabetes drugs or a placebo pill.

Glaxo disputed Dr. Nissen's conclusions, saying the overall body of evidence shows that Avandia is safe and effective.

Glaxo's stock continued to fall yesterday, dropping 1.4% in London to close at £13.71. On Monday the stock fell 5% in London trading.

Glaxo has been reviewing Avandia's safety since the drug hit the market in 1999 and last fall submitted new data on the drug to the FDA and the European Medicines Agency, or EMEA.

The EMEA looked at the data and concluded that there could be a risk for ischemic cardiac events

in patients taking Avandia, documents posted on the regulator's Web site show. A heart attack is one type of ischemic cardiac event. In September 2006, the EMEA updated its guidance for physicians to reflect the risk.

An EMEA spokeswoman said she couldn't comment on why the regulator acted differently from the FDA. She noted that in some cases the FDA adds warnings before EMEA and in other cases after. The EMEA decision didn't prompt much reaction in Europe. It isn't clear if it affected Avandia's sales.

The FDA is still reviewing the data Glaxo submitted, along with other data, to determine whether it needs to strengthen warnings on Avandia use. The agency on Monday said the data it is reviewing provide "contradictory evidence about the risks." The FDA said it plans to hold a special hearing to discuss the cardiovascular risks of Avandia and similar drugs "as soon as one can be convened."

A Glaxo spokeswoman yesterday said the company hasn't plans to change the way it markets Avandia. Glaxo in the past year has used mostly print and Internet advertising for Avandia. Glaxo this week has added a question-and answer-document about Dr. Nissen's study to the Web site www.avandia.com .

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URL for this article:
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EXHIBIT 40

FOCUS - 2 of 5 DOCUMENTS

THE WALL STREET JOURNAL.
The Wall Street Journal

May 31, 2007 Thursday

SECTION: HEALTH & FAMILY; Pg. D6

LENGTH: 459 words

HEADLINE: Glaxo Letter Defends Avandia

BYLINE: By Sarah Rubenstein

BODY:

GlaxoSmithKline PLC defended Avandia in a letter published on the Lancet medical journal's Web site, pointing to three studies to argue that the diabetes drug is safe for the heart.

Ronald Krall, chief medical officer, wrote in the letter that Glaxo did a "meta analysis" similar to the one conducted by Cleveland Clinic cardiologist Steven Nissen, whose article in the New England Journal of Medicine last week linked the drug to a potentially increased risk of heart attacks. Glaxo's own meta-analysis also found indications of increased risk, Dr. Krall wrote, but he said the number of adverse events was low.

Dr. Krall also discussed results from two large Glaxo-funded studies of the drug. Neither trial, called Dream and Adopt, was designed primarily to assess the drug's heart risks. But Glaxo's analysis of the Adopt trial showed major adverse cardiovascular events, such as heart attacks and strokes, were "rare," and heart risks were similar to those of two other diabetes drugs. The Dream trial also showed "no significant difference" in cardiovascular events between the drug and placebo, the letter said.

Meanwhile, an independent safety board recently reviewed an interim analysis of an ongoing study, Record, designed specifically to assess the drug's impact on the heart. The board determined the trial should continue, the Glaxo letter said.

In an interview, Christopher Viehbacher, Glaxo's president of U.S. pharmaceuticals, said the trial's interim results were "giving us the confidence to say that we stand behind this product." He said there is a chance the interim results will become public before the Record trial is complete, though the trade-off would be that the publicity could weaken the statistical power of the final results.

Mr. Viehbacher said it wouldn't surprise the company if the Food and Drug Administration were to call for "some labeling changes" for Avandia. One possibility would be elevating a heart-failure warning on the label to a more severe

"black box" warning, he said.

Dr. Nissen criticized Glaxo's letter to the Lancet, saying the company was slicing the data differently from the Adopt and Dream results originally published. Dr. Nissen also said the company was referring to such small subsets of data in the Adopt and Dream trials, that no firm conclusion could be drawn.

"Somebody went back and looked for something that would support their contention," Dr. Nissen said. "This is not a scientifically proper way to analyze data."

Mr. Viehbacher said that after Dr. Nissen's article was published last week, "we were shouting in a gale-force wind blowing against us." Now, he said, the public-relations situation was improving.

NOTES:
PUBLISHER: Dow Jones & Company, Inc.

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EXHIBIT 41

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

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ABSTRACT

BACKGROUND

A recent meta-analysis raised concern regarding an increased risk of myocardial infarction and death from cardiovascular causes associated with rosiglitazone treatment of type 2 diabetes.

METHODS

We conducted an unplanned interim analysis of a randomized, multicenter, open-label, noninferiority trial involving 4447 patients with type 2 diabetes who had inadequate glycemic control while receiving metformin or sulfonylurea, in which 2220 patients were assigned to receive add-on rosiglitazone (rosiglitazone group), and 2227 to receive a combination of metformin plus sulfonylurea (control group). The primary end point was hospitalization or death from cardiovascular causes.

RESULTS

Because the mean follow-up was only 3.75 years, our interim analysis had limited statistical power to detect treatment differences. A total of 217 patients in the rosiglitazone group and 202 patients in the control group had the adjudicated primary end point (hazard ratio, 1.08; 95% confidence interval [CI], 0.89 to 1.31). After the inclusion of end points pending adjudication, the hazard ratio was 1.11 (95% CI, 0.93 to 1.32). There were no statistically significant differences between the rosiglitazone group and the control group regarding myocardial infarction and death from cardiovascular causes or any cause. There were more patients with heart failure in the rosiglitazone group than in the control group (hazard ratio, 2.15; 95% CI, 1.30 to 3.57).

CONCLUSIONS

Our interim findings from this ongoing study were inconclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes. There was no evidence of any increase in death from either cardiovascular causes or all causes. Rosiglitazone was associated with an increased risk of heart failure. The data were insufficient to determine whether the drug was associated with an increase in the risk of myocardial infarction. (ClinicalTrials.gov number, NCT00379769.)

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*Investigators for the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study group are listed in the Appendix.

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FOR PATIENTS WITH TYPE 2 DIABETES, CARdiovascular disease is the leading cause of death and the major cause of morbidity.[1] In such patients, cardiovascular risk is considerably elevated,[2] although recent reports have moderated this concern.[3,4] Factors that are implicated in the development of atherosclerosis include dyslipidemia, obesity, hypertension, hyperglycemia, and hyperinsulinemia.[5]

Type 2 diabetes is a progressive disease and its prevalence in the population is increasing. Since there is greater attention to glycemic targets, more patients are receiving combination therapies. Clinical trials comparing monotherapies are common, but comparisons of new dual-agent combinations with the standard of metformin plus sulfonylurea are rare. The Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial is a long-term, multicenter, randomized, open-label study[6] that compares cardiovascular outcomes in patients with type 2 diabetes treated with rosiglitazone (Avandia) plus metformin or sulfonylurea (rosiglitazone group) with outcomes in patients treated with metformin plus sulfonylurea (control group). The results of the United Kingdom Prospective Diabetes Study (UKPDS) suggest that the comparators metformin and sulfonylurea used in the RECORD trial reduce myocardial infarction by 39% and 16%, respectively, as compared with conventional treatment and diet.[7,8]

After a recent meta-analysis by Nissen and Wolski[9] raised concern about the cardiovascular safety of rosiglitazone, the current totality of evidence needs to be made available. Accordingly, this interim report presents the outcomes and deaths from cardiovascular causes so far in the RECORD study.

METHODS

PATIENTS

The RECORD study has been described in detail previously.[6] We recruited patients for the study from April 2001 through April 2003. Eligible patients had type 2 diabetes, as defined by criteria of the World Health Organization[10]; were between the ages of 40 and 75 years; had a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 25.0; and had a glycated hemoglobin level of more than 7.0% and less than or equal to 9.0% while receiving maximum doses of metformin or a sulfonylurea. Exclusion criteria were the current use of other glucose-lowering agents, hospitalization for a major cardiovascular event in the previous 3 months, a planned cardiovascular intervention, heart failure, clinically significant hepatic disease, renal impairment, and uncontrolled hypertension. The study protocol was approved by ethics review committees or institutional review boards in accordance with the laws and customs of each country participating in the study.[6] Written informed consent was obtained from all patients.

STUDY DESIGN

The study is being conducted at 338 centers in 23 countries in Europe and Australasia. After a 4-week run-in period, patients who were already taking a sulfonylurea were randomly assigned to receive either additional rosiglitazone or metformin; those taking metformin were assigned to receive either additional rosiglitazone or a sulfonylurea (glyburide, gliclazide, or glimepiride, according to local practice). Random allocation was performed by telephone, with random permuted blocks stratified according to background medication.

Throughout the study, the target glycated hemoglobin level was 7.0% or less. The starting dose of rosiglitazone (Avandia, GlaxoSmithKline) was 4 mg per day. The starting doses of metformin and sulfonylurea were determined according to local practice. If the glycated hemoglobin level exceeded 7.0% after 8 weeks of treatment, the doses of study drugs were increased to a maximum daily dose of 8 mg of rosiglitazone, 2550 mg of metformin, 15 mg of glyburide, 240 mg of gliclazide, and 4 mg of glimepiride. If the glycated hemoglobin level exceeded 8.5% while patients were receiving the maximum tolerated dose, a third agent was added for patients in the rosiglitazone group or insulin was initiated for patients in the control group. If patients receiving triple therapy in the rosiglitazone group had glycated hemoglobin levels of more than 8.5%, the study protocol recommended that rosiglitazone be stopped and insulin therapy started.

OUTCOME MEASURES

The primary end point was hospitalization (for acute myocardial infarction, congestive heart failure, stroke, unstable angina pectoris, transient ischemic attack, unplanned cardiovascular revascularization, amputation of extremities, or any

other definite cardiovascular reason) or death from cardiovascular causes (including heart failure, acute myocardial infarction, sudden death, and death caused by acute vascular events including stroke); the outcome was analyzed as the time to first occurrence. Members of an independent committee evaluating clinical end points (five cardiologists, a neurologist, and a diabetologist) were unaware of study-group assignments and used prespecified criteria to adjudicate all potential outcomes reported by investigators. Evaluators in the trial's contract organization (Quintiles) were unaware of study-group assignments in screening all serious adverse events for porential end points.

This interim report evaluated data that were available as of March 30, 2007. Secondary end points were death from cardiovascular causes and from any cause, myocardial infarction (resulting in either hospitalization or death), congestive heart failure (hospitalization or death), and the composite of death from cardiovascular causes, myocardial infarction, and stroke. Some events were pending adjudication while this report was being written. Analyses are reported both for adjudicated events only and for adjudicated events plus events pending adjudication. For 19 cardiovascular deaths pending adjudication, we cannot determine yet whether any were due to acute myocardial infarction or congestive heart failure.

STUDY OVERSIGHT

An independent data and safety monitoring board meets twice annually to review unblinded safety data for the ongoing study; the most recent meeting took place on May 24, 2007. Members of the steering committee (seven academic investigators and one representative of the sponsor) developed the study design, had full access to the interim data, were responsible for the decision to publish the results, and wrote the manuscript. The committee members vouch for the accuracy and completeness of the data reported. Study committees and investigators are listed in the Appendix.

STATISTICAL ANALYSIS

The RECORD study was designed as a noninferiority trial. The rosiglitazone group was defined as noninferior to the control group if the upper limit of the two-sided 95% confidence interval for the hazard ratio for the primary end point comparing the rosiglitazone group with the control group was below 1.20 on completion of the study. A total of 4000 patients to be followed for a median of 6 years would give a power of 99% to detect such noninferiority when the control group had an event rate of 11% per year (3% with deaths from cardiovascular causes and 8% with hospitalizations), allowing for a 2% annual loss to follow-up.

This interim report follows a prespecified plan for statistical analysis. All analyses were performed according to the intention-to-treat principle, with the exclusion of 11 patients who received no study medication. The time from randomization to the event was derived for each end point, with follow-up censored at the cutoff date of March 30, 2007, for patients who did not have an event. Cumulative incidence was estimated with the use of the Kaplan–Meier method. The relative risk comparing the rosiglitazone group with the control group was estimated as a hazard ratio and 95% confidence interval on the basis of Cox proportional-hazards regression stratified according to background medication. Two-sided P values were calculated with the use of log-rank tests, unadjusted for multiple testing.

RESULTS

PATIENTS

Of 7428 patients who underwent screening, 4458 were randomly assigned to study groups (Fig. 1). No study medication was received by 11 patients (6 in the rosiglitazone group and 5 in the control group), who were excluded from the analysis. At baseline, 2222 patients who were receiving metformin monotherapy were assigned to receive either rosiglitazone plus metformin (1117 patients) or metformin plus sulfonylurea (1105 patients); 2225 patients receiving sulfonylurea monotherapy were assigned to receive rosiglitazone plus sulfonylurea (1103) or metformin plus sulfonylurea (1122). Results presented here are for all patients who were randomly assigned to receive rosiglitazone combinations (2220), as compared with all patients assigned to receive metformin plus sulfonylurea (2227).

Approximately 10% of patients (218 in the rosiglitazone group and 223 in the control group) were lost to follow-up. This fact, along with the much lower overall event rate than we had predicted, substantially lowered the statistical power of our analysis. A total of 140 patients in the rosiglitazone group and 244 patients in the control group began to receive insulin. At the latest visit, 1626 patients in the rosiglitazone group and 1476 patients in the control group were receiving their

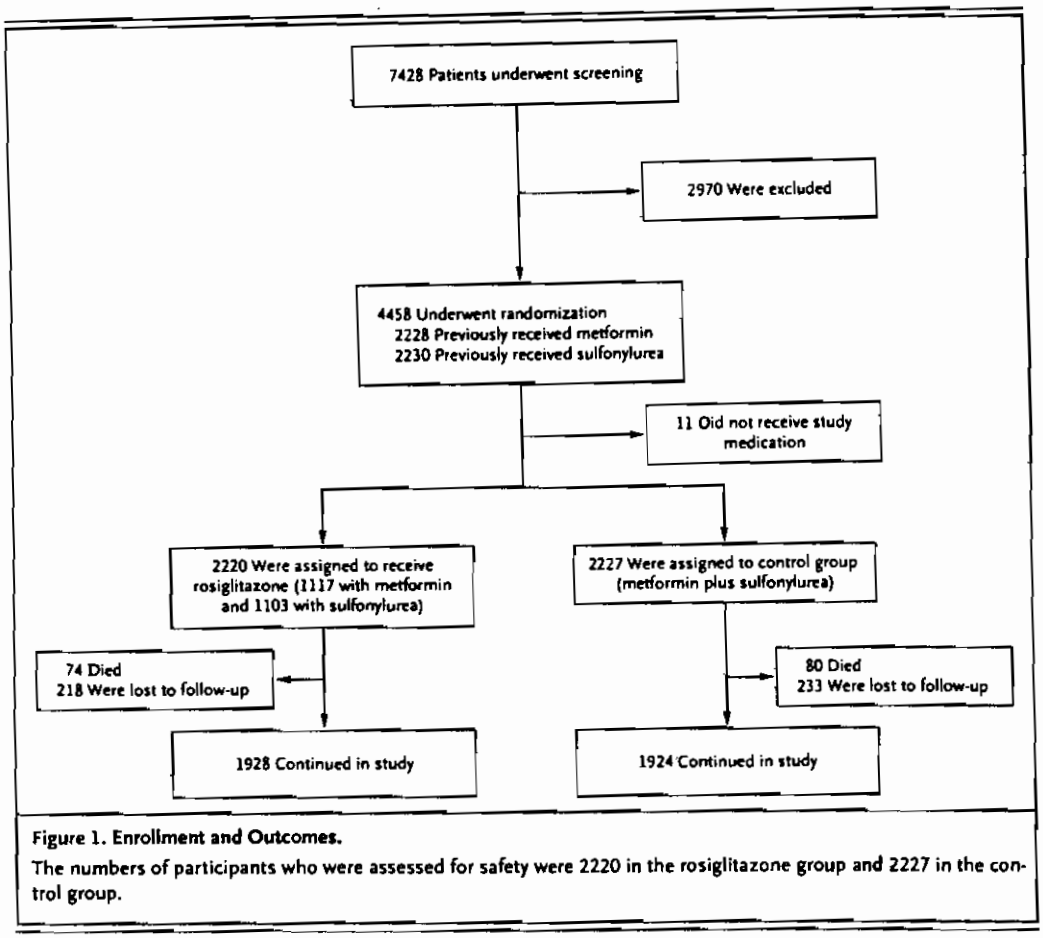

Figure 1. Enrollment and Outcomes.

The numbers of participants who were assessed for safety were 2220 in the rosiglitazone group and 2227 in the control group.

allocated treatment. In total, 675 patients (263 in the rosiglitazone group and 412 in the control group) withdrew from receiving study drugs but were still in follow-up.

Baseline characteristics were well balanced between the groups (Table 1). Table 2 shows by group the numbers of patients with the primary end point (hospitalization or death from cardiovascular causes) and several secondary end points over a mean follow-up of 3.75 years (3.77 years for the rosiglitazone group and 3.73 years for the control group). Results are reported for adjudicated events and for events adjudicated plus those pending adjudication. Kaplan–Meier plots are shown in Figures 2 and 3.

For adjudicated primary end points (217 in the rosiglitazone group and 202 in the control group), the hazard ratio was 1.08 (95% confidence interval [CI], 0.89 to 1.31). An additional 91 patients (50 in the rosiglitazone group and 41 in the control group) had potential primary events reported by investigators, but these events were pending adjudication. The inclusion of these events resulted in a hazard ratio of 1.11 (95% CI, 0.93 to 1.32). A subgroup analysis of patients who were classified according to previous monotherapy with metformin or sulfonylurea revealed no evidence of a treatment-by-stratum interaction (interaction test, P=0.41). The time-to-event curves in Figure 2 may suggest possible divergence between groups, with more events in the rosiglitazone group after 2.5 years of follow-up. However, data after 4 years involve small numbers of patients, and further follow-up will be necessary.

There was no statistically significant difference between the rosiglitazone group and the control group for the following secondary end points: acute myocardial infarction, death from cardiovascular causes or any cause, or the composite of cardiovascular death, myocardial infarction, and stroke (both for adjudicated events and adjudicated plus pending events). However, the power to detect

Table 1. **Baseline Characteristics of the Patients.***

Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)
Previous medication — no. (%)		
Metformin only	1117 (50.3)	1105 (49.6)
Sulfonylurea only	1103 (49.7)	1122 (50.4)
Age — yr	58.4±8.3	58.5±8.3
Male sex — no. (%)	1142 (51.4)	1152 (51.7)
White race — no. (%)†	2200 (99.1)	2199 (98.7)
Time since diagnosis — yr	7.0±5.0	7.1±4.9
Body-mass index	31.6±4.7	31.5±4.9
Glycated hemoglobin — %	7.9±0.7	7.9±0.7
Fasting plasma glucose — mg/dl	177±43	177±40
Hypertension — no. (%)‡	1754 (79.0)	1774 (79.7)
Ischemic heart disease — no. (%)		
Any disease	359 (16.2)	374 (16.8)
Stable angina	222 (10.0)	228 (10.2)
Myocardial infarction	102 (4.6)	114 (5.1)
Unstable angina	20 (0.9)	30 (1.3)
Cerebrovascular disease — no. (%)		
Any disease	100 (4.5)	97 (4.4)
Stroke	54 (2.4)	54 (2.4)
Transient ischemic attack	50 (2.3)	47 (2.1)
Peripheral arterial disease — no. (%)	124 (5.6)	131 (5.9)
Congestive heart failure — no. (%)	12 (0.5)	6 (0.3)
Lipid disorder — no. (%)§	2123 (95.6)	2100 (94.3)
Smoking history — no. (%)		
Current smoker	363 (16.4)	343 (15.4)
Former smoker	565 (25.5)	539 (24.2)

* Plus–minus values are means ±SD. The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Race was determined by the investigators.
‡ Hypertension was defined as a systolic blood pressure of more than 130 mm Hg or a diastolic blood pressure of more than 80 mm Hg.
§ A lipid disorder was defined by investigator-reported diagnosis or as a low-density lipoprotein cholesterol level of 100 mg per deciliter or more, a triglyceride level of 200 mg per deciliter or more, or a high-density lipoprotein cholesterol level of less than 40 mg per deciliter for men or less than 50 mg per deciliter for women.

significant differences was low, as reflected by the wide 95% confidence intervals (Table 2). The hazard ratio for death from cardiovascular causes for adjudicated plus pending events was 0.80 (95% CI, 0.52 to 1.24). For myocardial infarction, the hazard ratio for adjudicated plus pending events was 1.23 (95% CI, 0.81 to 1.86).

Patients in the rosiglitazone group had a significantly higher risk of congestive heart failure than did patients in the control group, with 38 versus 17 adjudicated events (hazard ratio, 2.24; 95% CI, 1.27 to 3.97). The inclusion of events pending adjudication increased the number of events to 47 and 22, respectively (hazard ratio, 2.15; 95% CI, 1.30 to 3.57), resulting in an excess risk of heart failure in the rosiglitazone group of 3.0 (95% CI, 1.0 to 5.0) per 1000 patient-years of follow-up.

DISCUSSION

Since patients with type 2 diabetes have a high risk of cardiovascular disease, any hypoglycemic agent the patient receives should not worsen that risk and preferably should lower it. Although the RECORD study is ongoing, we believe the exceptional circumstances surrounding a recent safety concern regarding rosiglitazone make it important to publish interim data.

A recent meta-analysis by Nissen and Wolski raised concern that rosiglitazone was associated with an increased risk of myocardial infarction and death from cardiovascular causes.[9] The limitations of the meta-analysis have been pointed out by its authors and by others.[11] Many contributing studies were small-scale and short-term, were designed to evaluate glycemic control, had no event adjudication, and had an imbalance in follow-up (with more patients in the control group withdrawing owing to hyperglycemia). Trials with no myocardial infarctions and no deaths from cardiovascular causes were excluded, and rates of myocardial infarction were low.[12]

The RECORD trial is a large, randomized, long-term study involving patients with type 2 diabetes that was designed to assess the cardiovascular safety of rosiglitazone combined with metformin or sulfonylurea, as compared with the combination of metformin and sulfonylurea, medications with previous evidence of a reduction in cardiovascular risk.[7,8] All cardiovascular end points that are reported by investigators in the trial undergo independent blinded adjudication to enhance the quality of the data. A wide variety of patients with type 2 diabetes, with and without previous cardiovascular disease, are included in the study.

This interim report is based on data for 4447 participants with a mean follow-up of 3.75 years, representing 16,675 patient-years of follow-up — almost two thirds of the follow-up that was in-

Table 2. Hospitalization or Death from Cardiovascular Causes.*

Variable	Rosiglitazone Group (N = 2220)	Control Group (N = 2227)	Hazard Ratio (95% CI)	P Value
	no. of patients			
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

* Each patient was counted only once for each category. The primary end point was the first occurrence of a hospitalization or death from cardiovascular causes.

† Of the adjudicated deaths from cardiovascular causes, 38 (16 in the rosiglitazone group and 22 in the control group) were primary end points. The remainder occurred after the patient had already been hospitalized for a cardiovascular event. For deaths from cardiovascular causes that were adjudicated or pending adjudication, 47 (20 in the rosiglitazone group and 27 in the control group) were primary end points.

‡ This category included both hospitalizations and deaths. Some of the 19 deaths from cardiovascular causes (8 patients in the rosiglitazone group and 11 in the control group) that were pending adjudication may have been due to acute myocardial infarction or congestive heart failure, but these data were not available at the time of the study cutoff.

tended by the end of the study. The study design calls for targeting similar glycemic control in the rosiglitazone group and the control group to assess cardiovascular safety independent of glycemia. Patients and investigators are encouraged to follow a carefully planned treatment algorithm. A recent report on the first 1122 patients showed that patients in the rosiglitazone group and the control group had similar glycemic control after 18 months of treatment.[13]

Overall, the rate of primary end points (hospitalization or death from cardiovascular causes) was low: 3.1% per year for adjudicated plus pending events. The protocol excluded some high-risk patients (e.g., those with heart failure, hospitalization for cardiovascular causes during the previous 3 months, and pending cardiovascular intervention). Targeting treatment toward current management guidelines for dyslipidemia, hypertension, and improved glucose control may also contribute to the low event rate. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD, ISRCTN number 64783481) study reported an increase from 0 to 36% in the use of lipid-lowering therapy in its control group during 1998–2005.[14] This finding reflects guidelines that patients should be actively treated to reduce cardiovascular risk, notably with glucose-lowering drugs, statins, aspirin, and more intensive use of blood-pressure–lowering agents.[15] Moreover, event rates in recent similar trials involving patients with diabetes — the Collaborative Atorvastatin Diabetes Study (CARDS,[4] NCT00327418), Heart Protection Study (HPS,[3] ISRCTN 48489393), and FIELD[14] — are similar to those in the RECORD trial.

The interim results for the primary end point were inconclusive, with a hazard ratio of 1.08 (95% CI, 0.89 to 1.31) on the basis of events ad-

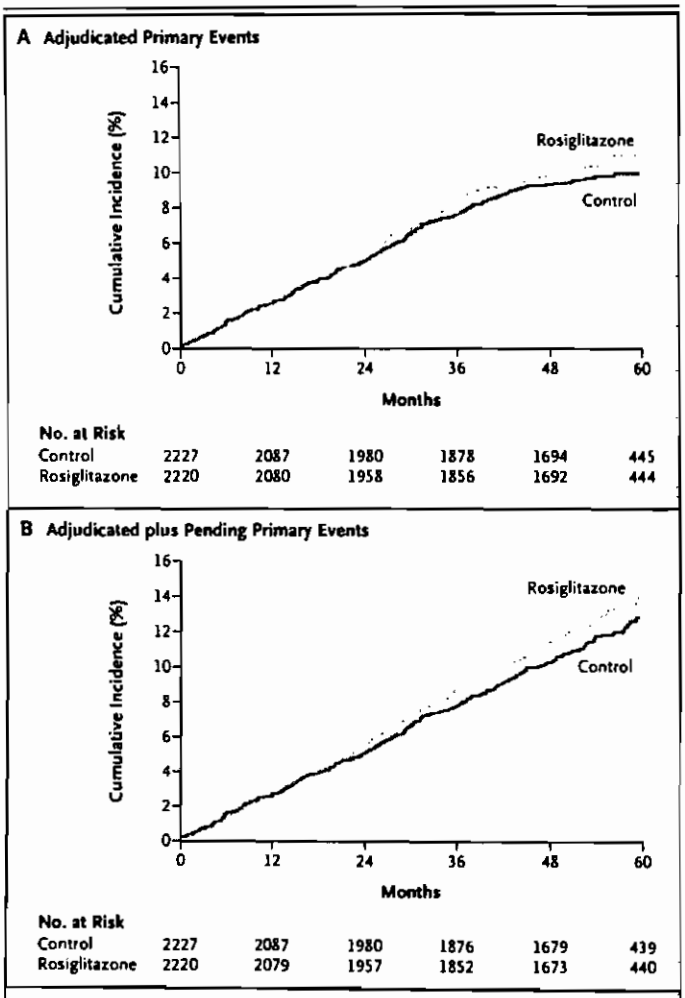

Figure 2. Kaplan–Meier Analysis of the Primary End Point of Hospitalization or Death from Cardiovascular Causes.

The graph shows the adjudicated events in the study (Panel A) and the adjudicated events plus events that were pending adjudication at the time of the study cutoff (Panel B).

judicated by the committee reviewing clinical end points. In any interim trial report, there are inevitably some potential primary events pending adjudication. Adding in these pending events increased the hazard ratio to 1.11 (95% CI, 0.93 to 1.32). Thus, the data for the primary end point are compatible with as much as a 7% improvement, or as much as a 32% worsening, in cardiovascular risk. The study lost statistical power because of the withdrawal of patients from their assigned treatment and losses to follow-up, although patients in the rosiglitazone group fared better in these respects than did patients in the control group. We cannot determine whether some consequent bias in end-point ascertainment occurred. All serious adverse events were screened for possible end points.

The low rate of the primary end point, along with the notable loss to follow-up, meant that the study has less statistical power than was originally planned. Assuming a continued primary-event rate of 3.1% per year, we project that 750 patients will have a primary end point by study completion. Under the hypothesis of no true treatment difference, this estimate would provide a power of 70% to claim noninferiority relative to a noninferiority margin of 1.20 for the hazard ratio. However, we already have 510 patients with a primary event (adjudicated plus pending events) and an observed hazard ratio of 1.11, which means that the conditional power to claim noninferiority on study completion is somewhat less.

As compared with the control group, the rosiglitazone group had no evidence of an increased risk of death, either from any cause (hazard ratio, 0.93; 95% CI, 0.67 to 1.27) or from cardiovascular causes (hazard ratio, 0.80, 95% CI, 0.52 to 1.24). The primary end point included all first hospitalizations or deaths from cardiovascular causes and as such included myocardial infarction and congestive heart failure. Our study showed that the risk of heart failure in the rosiglitazone group was more than twice that in the control group. This finding is consistent with previous evidence regarding heart failure and the thiazolidinediones.[16,17] Although the absolute excess risk was relatively small, this finding is of concern and reinforces advice that patients should be warned of the risk and that thiazolidinediones should not be started or continued in patients with heart failure.

For acute myocardial infarction, the difference between the rosiglitazone group and the control group was not statistically significant (hazard ratio for adjudicated events, 1.16; 95% CI, 0.75 to 1.81; hazard ratio for adjudicated plus pending events, 1.23; 95% CI, 0.81 to 1.86). These estimates are somewhat lower than those reported in the meta-analysis by Nissen and Wolski.[9] They are consistent with as much as a 19% improvement, and as much as an 86% worsening, in risk. For the composite end point of death from cardiovascular causes, myocardial infarction, and stroke, the rosiglitazone group did not differ significantly from the control group.

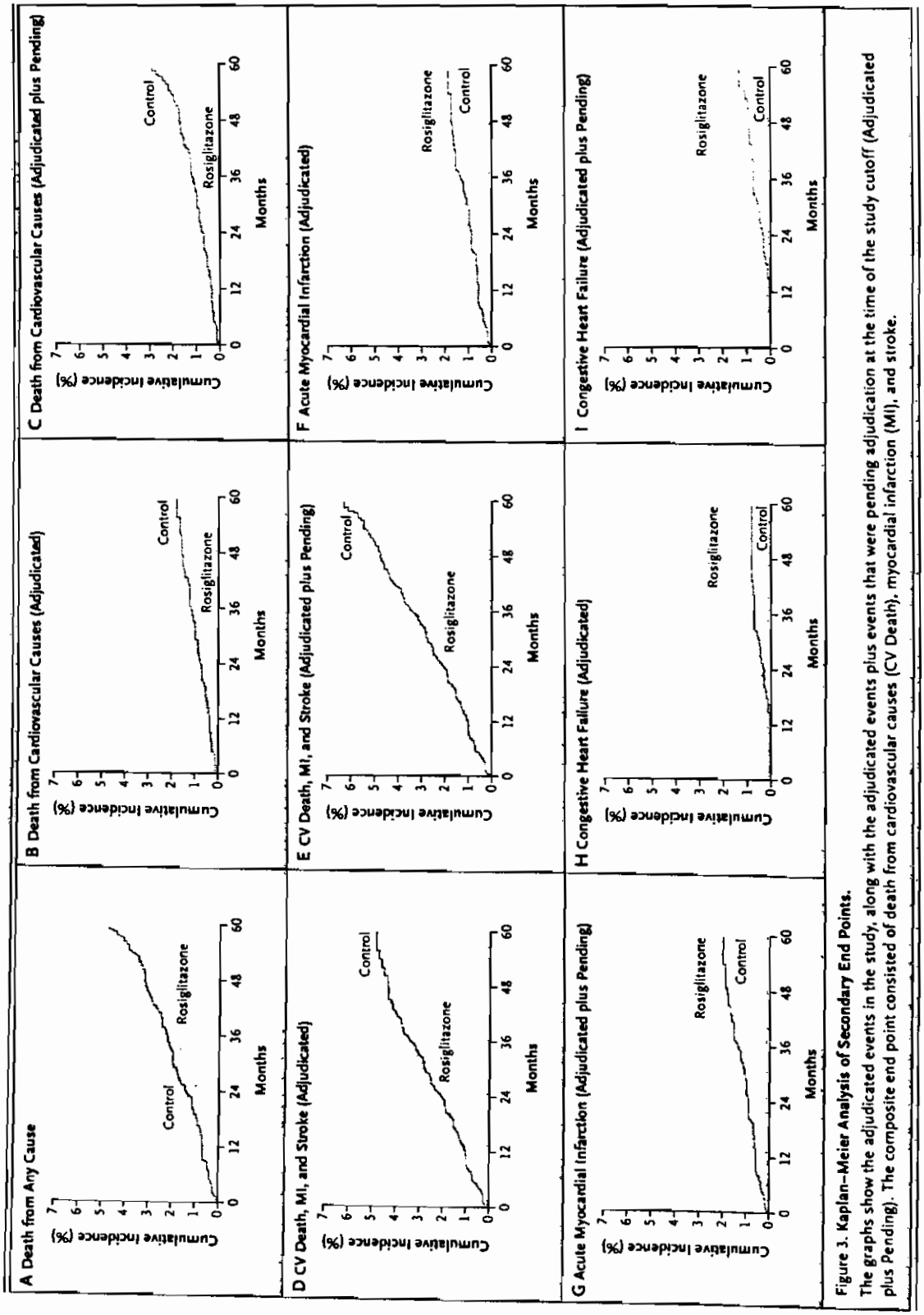

Figure 3. Kaplan–Meier Analysis of Secondary End Points.
The graphs show the adjudicated events in the study, along with the adjudicated events plus events that were pending adjudication at the time of the study cutoff (Adjudicated plus Pending). The composite end point consisted of death from cardiovascular causes (CV Death), myocardial infarction (MI), and stroke.

A significant limitation of our study was that it was an open-label trial. The allocation of drugs was nonblinded owing to the number of preparations and dosing schedules and because the time for the introduction of insulin therapy differed between groups. Monitoring staff checked site records for missing events, and all serious adverse events underwent blinded screening for potential cardiovascular end points; in addition, the adjudication of events was blinded. These procedures and the choice of end points reduce, but do not remove, the risk of ascertainment bias.

The primary composite end point reflects the study objective — an assessment of overall cardiovascular safety — but therefore includes some hospitalizations (e.g., for valvular disease) that no observer would consider potentially related to treatment. The inclusion of such events tends to favor the achievement of noninferiority. Hence, sensitivity analyses will be performed at the end of the study that include only events related to atherosclerotic arterial disease.

We made the decision to publish our interim findings because in their absence, concern raised by the meta-analysis by Nissen and Wolski could well compromise the study's integrity through an increase in the dropout rate and potential biases in reporting events. At present, every effort is being made to maintain follow-up until study completion in 2 years. Extra inquiries to investigators, to identify any end points previously missed,[18] are expected to reduce substantially the extent of loss to follow-up by the end of the study.

This interim analysis is restricted to a limited amount of information. The statistical plan was predefined. The intent was primarily to estimate treatment differences, with no planned action regarding study continuation, so the significance level of the final analysis was not affected. The final report will be more extensive, with data presented for different background medications and other subgroups and examining possible imbalances across treatment groups for concomitant medications and other possible confounders.

In conclusion, our interim findings from a large, prospective trial are inconclusive with respect to the primary end point of hospitalization or death from cardiovascular causes and are as yet insufficient to claim noninferiority. There is no evidence of any increased mortality, either from any cause or from cardiovascular causes. There is a significant increase in the risk of heart failure. The data do not allow a conclusion as to whether treatment with rosiglitazone results in a higher rate of myocardial infarction than does therapy with metformin or a sulfonylurea. The study's data and safety monitoring board, which is charged with safeguarding the study patients, has recommended continuation of the trial. Study completion will enable a clearer determination of the long-term cardiovascular effects of treatment with rosiglitazone and thus help determine the most appropriate combination therapies for patients with type 2 diabetes.

Supported by GlaxoSmithKline.

Dr. Home reports being involved in research, consulting, health care development, and teaching activities for all major pharmaceutical companies active in diabetes research (including GlaxoSmithKline), but all consulting and lecture fees he receives are donated to the institutions with which he is associated (Newcastle University, Worldwide Initiative for Diabetes Education, and the International Diabetes Federation); Dr. Pocock, receiving consulting fees and grant support from GlaxoSmithKline; Dr. Beck-Nielsen, receiving consulting fees from GlaxoSmithKline, Merck, and Novartis and grant support and lecture fees from GlaxoSmithKline and Novo Nordisk; Dr. Gomis, receiving consulting and lecture fees from GlaxoSmithKline, Novartis, Pfizer, Merck, and Sanofi-Aventis; Dr. Hanefeld, receiving consulting fees from GlaxoSmithKline, Novo Nordisk, and Sanofi-Aventis and lecture fees from Bayer-AG, Sanofi-Aventis, Hoffmann–La Roche, Takeda, and Eli Lilly; Mr. Jones, being an employee of and holding stock in GlaxoSmithKline; Dr. Komajda, receiving consulting fees from GlaxoSmithKline and Servier and lecture fees from GlaxoSmithKline and Takeda; and Dr. McMurray, receiving consulting fees from GlaxoSmithKline and Amgen and grant support from GlaxoSmithKline, Novartis, and Amgen. No other potential conflict of interest relevant to this article was reported.

We thank the study patients for their time and continued commitment; members of the data and safety monitoring board and clinical end-points committee for their diligent activity; Professor Henry Dargie for important and material contributions to the design and direction of the study; Dr. Duolao Wang for conducting confirmatory statistical analyses; and the GlaxoSmithKline and Quintiles RECORD teams for their quality input.

APPENDIX

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EXHIBIT 42

1 of 1 DOCUMENT

THE WALL STREET JOURNAL.
The Wall Street Journal

July 9, 2007 Monday

SECTION: Pg. B1

LENGTH: 1308 words

HEADLINE: Boss Talk: Glaxo's Garnier Is Taking the Heat --- Defending Safety of Avandia Preoccupies, But Doesn't Consume, Drug Company's CEO

BYLINE: By Jeanne Whalen

BODY:

Jean-Pierre Garnier, chief executive of GlaxoSmithKline PLC, has been in the hot seat since May, when an article in the New England Journal of Medicine raised concerns about the safety of the diabetes treatment Avandia, his company's second-biggest selling drug.

In the article, cardiologist Steven Nissen analyzed 42 past clinical trials of Avandia -- an approach known as a meta-analysis -- and concluded that patients taking the drug may be at a higher risk for heart attacks than patients taking other drugs. Since then, Avandia prescriptions have fallen sharply, and Glaxo's stock price has plummeted.

Dr. Garnier is now trying to fight research with research. He says Glaxo performed its own meta-analysis of Avandia before Dr. Nissen's -- and also found a risk of heart attack. But the risk was very slight, and was outweighed by other evidence showing that Avandia is as safe for the heart as other diabetes drugs, Dr. Garnier says. The Food and Drug Administration is now carrying out its own meta-analysis and will convene a panel of medical advisers on July 30 to weigh the evidence.

Dr. Garnier has faced safety crises before. In 2004, medical experts raised concerns that Glaxo's Paxil and other antidepressants could induce suicidal thinking and behavior in children, leading the FDA to add strong warnings to the drugs.

In an interview in Glaxo's Philadelphia office, Dr. Garnier discussed such topics as managing the Avandia crisis, the pricing of HIV drugs, serving poor communities and what he wants to accomplish before stepping down as CEO in May 2008. Excerpts follow.

WSJ: Has Glaxo done everything it could to study Avandia and communicate its risks to the public?

Dr. Garnier: We're not perfect, I'm sure. With 20-20 hindsight we could have done more. But I have to say in the case of Avandia, you see that we were diligent from the day of the launch to start to study the drug in some depth in [clinical] studies and then we did the meta-analysis a year ahead of Dr. Nissen.

As soon as we found out that there was at least a question raised by the meta-analysis, we immediately did the epidemiology study with 30,000 patients that came out absolutely squeaky clean and supportive of Avandia. So you look at the totality, Avandia is by far the most studied diabetic agent on the market today. So sure, maybe we could do more, but frankly the record is very good. Not only have we studied this drug right, left and center, but also we have been transparent, informed everybody.

WSJ: What feedback are you getting from doctors about Avandia?

Dr. Garnier: Doctors are worried about being sued for putting patients on Avandia and things like this. But overall, they are staying behind Avandia. Very few patients actually are switching off their medication. But some have.

WSJ: Are doctors more concerned about liability risk when putting new patients on the drug?

Dr. Garnier: Physicians are naturally gun-shy about putting new patients on. The reality is, and we have the data, they're putting fewer new patients on it.

We've just run a big survey of physicians, and they're playing back again the two key points: "Most of my patients have not switched, and I have no intention of switching them. However, as far as putting new patients on Avandia, I'm putting far fewer than before, and I'm waiting to see what the FDA has to say."

WSJ: Does the safety flap take up your entire day?

Dr. Garnier: Pretty much, 24-7. This is a very unpleasant event. But on the other hand this is not my first one. I've been there before. My job is to manage the company through the crisis.

WSJ: How do you do that?

Dr. Garnier: We have crisis-management phone calls every day. These things don't get done without a lot of coordination.

WSJ: Glaxo recently donated 50 million pandemic flu vaccines to the World Heath Organization. What's the story?

Dr. Garnier: It's probably the largest vaccine donation ever. The company could have sold possibly those 50 million units. They [Glaxo] decided to set them aside because frankly those countries are not going to buy any pandemic vaccine. Some of them have no commitment to health care.

Let's call a cat a cat. They'll buy a lot of other things including Kalashnikovs before they allocate enough money for health care in their own countries. [Some] are committed to better health care but [pandemic flu] never makes their top 10 list because they have humongous problems. They have HIV, and they have this and that. So putting resources aside for a maybe problem doesn't work out to their top priority.

WSJ: How has Glaxo changed its HIV-drug pricing in the developing world since you started running the company?

Dr. Garnier: I always wanted to have access as part of the DNA of the company. I don't look at those things as philanthropic undertakings. Even Tykerb -- we just introduced this breast-cancer treatment in the U.S. It's a very expensive product for the average person. We provide funding and subsidies for people up to an income level of $100,000 per family. It's intertwined with the purely commercial pricing. I wanted that. I never wanted to just close my eyes to the fact that 80% of the population won't be able to afford the drugs. Because that's the truth -- 80% of the

market for pharmaceuticals comes from 20% of the world-wide population. I'm not going to be CEO of a company that just works for rich countries. And even within rich countries, by the way, you have holes in the safety net that are part of the equation.

WSJ: What has that meant in HIV?

Dr. Garnier: To me, it became very obvious that we had to go much further than to give discounts [on drugs]. We had to make basically a philosophical statement that for the very poor countries of this world, we were going to sell our drugs without making a profit, completely not for profit. And overnight we did this. And that allowed the consumption of HIV drugs in Africa to increase dramatically, exponentially. Overnight we went from very little to hundreds and hundreds of millions of tablets. Then we went one step further and said, why don't we give licenses to generic companies [to make our drugs], particularly local companies. Maybe they can make it even cheaper.

WSJ: What are the main things Glaxo has done to provide better access [to HIV drugs] and what's been the effect?

Dr. Garnier: What we sell at this not-for-profit price corresponds to roughly a million patients being treated, mostly in Africa.

We dropped the price, helped with access -- that is, we have a number of community support programs. Because treating people who have HIV is not a simple thing.

WSJ: What are you doing? Opening clinics? Hiring doctors?

Dr. Garnier: No, we don't own the infrastructure but we've supported clinics. Not just with money -- with advice, sending doctors.

WSJ: Do you do much licensing for production of your drugs in middle-income countries like Thailand?

Dr. Garnier: No, no, no. Middle-income countries should pay a fair price for our drugs. They certainly can use some of their resources to pay a fair price, which is clearly an intermediate price between the lowest and the highest -- we try to price according to standard of living.

WSJ: You're retiring next year. What more do you want to do?

Dr. Garnier: No. 1 is deliver the pipeline. We have a very exciting, high-quality, deep, dense, innovative pipeline of late-stage drugs. So let's make sure we deliver, and those drugs pass the last hurdle and get launched.

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5 Tips from Jean-Pierre Garnier on managing through a crisis:

-- 1: Fight data with data.

-- 2: Communicate to employees. Daily phone calls are essential.

-- 3: Study doctor opinion to catch any changes.

-- 4: Put data on company Web site so everyone can see.

-- 5: Keep working on long-term business goals.

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EXHIBIT 43

American Heart Association.
Learn and Live.

Cardiac Glossary

A–C D–O P–Z

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Click on the image to see a detailed medical illustration.

Ablation — Cardiac ablation is a therapeutic method in which a form of energy is used to physically destroy a small section of damaged heart tissue that is a source of abnormal electrical activity causing or contributing to some types of tachycardia (fast heartbeat). Most often, cardiac ablation is used to treat rapid heartbeats that begin in the upper chambers (atria) or in the atrioventricular (AV) node. Less often, ablation is used to treat heart rhythm disorders of the lower heart chambers (ventricles). It may be done through surgery or using a transcatheter approach with an electrode catheter (catheter ablation). Electrodes at the catheter tip are used to help identify the site of abnormal activity. The electrode then delivers either radiofrequency energy (RF ablation) or intense cold (cryoablation) to destroy the small section of tissue.

Abnormal Glucose Tolerance — The inability to metabolize (use) sugar adequately.

Adenosine — A naturally occurring substance produced in many sites in the body that plays a role in important biochemical processes. It can cause dilation (widening) of coronary arteries as well as many other effects throughout the body such as regulating heart rhythm, toning blood vessels, maintaining wakefulness and producing urine. As a drug, adenosine is used to treat some types of arrhythmias (abnormal heart rhythms), specifically those that cause a fast heartbeat.

Advance Directive — A written document that states a person's healthcare choices and names someone to make those choices, should the person become unable to make their own decisions about medical care. The most common types of Advance Directives are a living will and a durable power of attorney for health care.

Aldosterone — A hormone released by the adrenal glands that works on the kidneys to help the body retain sodium and excrete potassium. It is the main regulator of the salt and water balance in the body. It also acts on the central nervous system to increase a person's appetite for salt and to make them feel thirsty. These effects directly act to increase the amount of fluid in the blood and to increase blood pressure.

Aldosterone Antagonist (Aldosterone Receptor Blocker), (Diuretic) — Drugs that act as diuretics (water pills) by blocking the body's response to the hormone aldosterone. Aldosterone promotes the retention of sodium and the excretion of potassium. Aldosterone antagonists increase urination, reducing water and salt while retaining potassium. They help lower blood pressure, increase the heart's pumping ability and help protect the heart in heart failure.

Alpha Blockers — A group of drugs used to lower blood pressure. They do this by blocking the effects of certain chemicals or hormones (specifically adrenaline or adrenaline-like substances) on alpha receptors (parts of cells that trigger physiological changes in the body). These changes can speed the heart, strengthen the heartbeat and constrict the blood vessels. These reactions cannot be triggered if the alpha blockers block the chemicals. (Also known as alpha-adrenergic antagonists, alpha-adrenergic blocking agents, and alpha-adrenergic blockers.)

Amiodarone — A Class III antiarrhythmic drug (potassium channel blocker) used to slow the heart rate and help keep it in a regular rhythm. It is used to treat fast and/or irregular heart rates from the heart's upper and lower chambers including atrial fibrillation, ventricular tachycardia and ventricular fibrillation. Side effects are usually dose-related and regular follow-up is necessary to determine kidney, liver and lung function.

Anemia — A reduction in the amount of oxygen-carrying red blood cells. Anemia can have many causes, but the most common is a lack of iron in the body. Also known as iron-poor blood.

Anesthesiologist — A physician specializing in the practice of anesthesiology and the use of anesthetic medicines. These medications result in a loss of sensation, memory, pain and consciousness and are used during surgical procedures.

Aneurysm — An abnormal widening or ballooning-out of the wall of an artery, a vein or the heart due to weakening of the wall by disease, injury or an abnormality present at birth. Some common locations for aneurysms include the aorta (the major artery leading away from the heart), brain (cerebral aneurysm), leg, intestine and splenic artery.

Angina Pectoris (Angina) — Medical term for chest pain or discomfort due to coronary heart disease. Angina is a symptom of a condition called myocardial ischemia. It occurs when the heart muscle (myocardium) doesn't get as much blood (hence as much oxygen) as it needs for a given level of work. Insufficient blood supply is called ischemia. **Stable angina** (or chronic stable angina) refers to "predictable" chest discomfort such as that associated with physical exertion or mental or emotional stress. Rest and/or nitroglycerin usually relieve stable angina. **Unstable angina** refers to unexpected chest pain and usually occurs at rest. It is typically more severe and prolonged and is due to a reduced blood flow to the heart caused by the narrowing of the coronary arteries in atherosclerosis. **Unstable angina is an acute coronary syndrome and should be treated as an emergency.**

Angiogenesis — The creation of blood vessels. The body creates small blood vessels called "collaterals" to help compensate for reduced blood flow.

Angiography — An X-ray test used to detect and diagnose diseases of the blood vessels, such as weakening of the vessel walls and the narrowing or blocking of vessels, and to examine the chambers of the heart. The X-ray is taken after the vessels have been injected with a substance (dye) that allows them to be seen on film. The pictures that are obtained are called angiograms. Coronary angiography is done during a cardiac catheterization. (Also known as Angiocardiography, Angiogram and Arteriography.)

Angioplasty — A medical procedure in which a balloon is used to open narrowed or blocked blood vessels of the heart (coronary arteries). It is not considered to be a type of surgery. A catheter with a deflated balloon on its tip is passed into the narrowed artery segment, the balloon is inflated and the narrowed segment widened. Then the balloon is deflated and the catheter is removed. (Also known as Percutaneous Transluminal Coronary Angioplasty (PTCA), Percutaneous Coronary Intervention (PCI), Balloon Angioplasty, and Coronary Artery Balloon Dilation.)

Angiotensin — A chemical produced by the body that acts as a vasoconstrictor, causing the muscles around the blood vessels to contract, thus narrowing the blood vessels. This can cause high blood pressure. Angiotensin also stimulates aldosterone secretion.

Angiotensin-Converting Enzyme (ACE) Inhibitors — A class of drugs used to treat high blood pressure and heart failure. ACE inhibitors stop the body's production of angiotensin, which lowers blood pressure, increases blood flow to the heart and reduces the heart's workload.

Angiotensin II Receptor Blockers (or Inhibitors) (ARBs) — A class of drugs used to treat high blood pressure and heart failure. They do not interfere with the body's *production* of angiotensin. They block the *effects* of angiotensin, preventing it from constricting the muscles around the blood vessels and

narrowing the blood vessels. In this way they keep the coronary arteries open, which lowers blood pressure, increases blood flow to the heart and reduces the heart's workload. (Also known as Angiotensin-2 Receptor Antagonists)

Ankle-brachial Index (ABI) Test— A painless exam that compares the blood pressure in the feet to the blood pressure in the arms to determine how well the blood is flowing. This test is used to diagnose peripheral artery disease (PAD). It takes only a few minutes and can be performed by a healthcare professional as part of a routine exam.

Antiarrhythmic Medication — A group of drugs that helps control and slow heart rate. They do this by either suppressing (slowing) the activity of tissue that is initiating electrical impulses too quickly in the heart's natural pacemaker (the sinoatrial or SA node) or by slowing the transmission of fast electrical impulses inside the heart. Antiarrhythmics include several classes of drugs such as sodium channel blockers, beta-blockers, potassium channel blockers, calcium channel blockers, adenosine and digitalis (also called digoxin and digitoxin). The type of arrhythmia you have determines which medication will be prescribed.

Anticoagulant (Blood Thinners) — A group of drugs that decrease the ability of the blood to clot, or coagulate. They are sometimes called blood thinners, although they do not actually thin the blood. They are used to treat certain blood vessel, heart and lung conditions. They are also given to certain people at high risk for forming blood clots, such as those with artificial heart valves or who have atrial fibrillation. Anticoagulants do not dissolve clots but may prevent existing clots from becoming larger and causing more serious problems, and are often prescribed to prevent first or recurrent heart attack or stroke. Common anticoagulant drugs are heparin and warfarin.

Antihypertensive Drugs — A group of drugs commonly prescribed to help lower blood pressure when appropriate diet and regular physical activity alone have not succeeded. They include diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARBs), vasodilators, alpha-blockers, beta-blockers, calcium channel blockers and central alpha-agonists. Many patients with high blood pressure may require more than one drug to achieve control. Some of these drugs may also be prescribed for heart failure and arrhythmia patients.

Antiplatelet Agents — A group of drugs used to keep blood clots from forming by preventing blood platelets from sticking together. They help prevent clotting in patients who have had a heart attack, unstable angina, ischemic strokes, transient ischemic attacks (TIA) and other forms of cardiovascular disease. They are usually prescribed preventively, when plaque buildup is evident in the arteries but there is not yet a large obstruction. Aspirin and clopidogrel are examples.

Aorta — The large artery that receives blood from the heart's left ventricle and distributes it to the body.

Aortic Stenosis (AS) — A congenital heart defect in which the aortic valve, between the left ventricle and the aorta, is narrowed. It occurs when the aortic valve didn't form properly. Sometimes stenosis is severe and symptoms occur in infancy. Otherwise, most children with aortic stenosis heve no symptoms. In some children, chest pain, unusual tiring, dizziness or fainting may occur. The need for surgery depends on how severe the stenosis is. A procedure called balloon valvuloplasty has been used in some children. Children with aortic stenosis need lifelong medical follow-up.

Aortic Valve — The heart valve between the left ventricle and the aorta. It has three flaps (cusps).

Aphasia — A total or partial loss of the ability to use words. It may be caused by brain injury or disease. It's most often caused by a stroke that injures the brain's language center. Some people with aphasia recover quickly and completely after a stroke. Others may have permanent speech and language problems.

Arrhythmia (Dysrhythmia) — An abnormal heartrhythm caused by a disruption of the normal functioning of the heart's electrical conduction system. Normally, the atria and ventricles contract in a coordinated manner. Arrhythmias result in

or longer depending on the monitor used. Electrodes (small conducting patches) are placed on the chest and attached to a small recording monitor that is carried in a pocket or in a small pouch worn around the neck. The recording is then analyzed, a report of the heart's activity is tabulated and irregular heart activity is correlated with a diary that is kept of the person's activity at the time. It is very important that symptoms and activities are accurately recorded so that the doctor can correlate them with the Holter monitor findings. (Also called Ambulatory Electrocardiography, Ambulatory ECG or Ambulatory EKG.)

Home-Based Healthcare — In-home care for ongoing medical conditions, usually by visiting nurses. This might include intravenous antibiotics, physical assessment, etc.

Homocysteine — An amino acid naturally found in the blood that may serve as a marker for higher risk of coronary artery disease (CAD), stroke and peripheral vascular disease.

Homograft — Material (usually human heart valves and arteries) donated from a cadaver to be used during complex reconstructive surgery.

Hypercholesterolemia — High levels of blood cholesterol, a major risk factor for coronary heart disease, heart attack and stroke.

Hypertension — Medical term for high blood pressure. **(See High Blood Pressure)**

Hyperthyroidism — Overactivity of the thyroid gland, leading to overproduction of thyroid hormones. It can make the body's metabolism overactive, leading to symptoms such as weight loss and rapid heart rate.

Hypertriglyceridemia — High levels of triglycerides in the blood. A high triglyceride level combined with low HDL cholesterol or high LDL cholesterol seems to speed up atherosclerosis (fatty buildups of plaque in the arteries). A normal triglyceride level is less than 150 mg/dL.

Hypoplastic Left Heart Syndrome — A congenital defect in which the left side of the heart is underdeveloped — including the aorta, aortic valve, left ventricle and mitral valve. Blood returning from the lungs must flow through an opening in the wall between the atria, called an atrial septal defect. The right ventricle pumps the blood into the pulmonary artery, and blood reaches the aorta through a patent ductus arteriosus. Babies with this syndrome often seem normal at birth, but will come to medical attention within a few days of birth as the ductus closes. They become ashen, have rapid and difficult breathing and have difficulty feeding. It is usually fatal within the first days or months of life without treatment, which can include a heart transplant.

Hypotension —The medical term for abnormally low blood pressure.

Hypothermic Circulatory Arrest — During open-heart surgery, especially in neonates and young children, the body temperature can be lowered to 60–65°F and the heart/lung machine turned off ("circulatory arrest"). This allows the surgeon to most precisely operate on a still (non-beating) heart, in an operative field where cardiac structures can best be seen.

Implantable Cardioverter Defibrillator (ICD) — An internal defibrillator used in patients at risk for recurrent, sustained ventricular tachycardia or fibrillation. ICDs look similar to a pacemaker and are about the size of a pocket watch. They continuously monitor the heart rhythm to detect overly rapid arrhythmias. The ICD corrects the heart rhythm by delivering precisely calibrated and timed electrical shocks to restore a normal heartbeat when one of these dangerous arrhythmias has occurred. ICDs run on batteries and can last many years.

Incidence — The number of new cases of a disease that develop in a population during a one-year period. For some statistics, new and recurrent attacks or cases are combined.

Inferior Vena Cava — A major vein that carries blood from the lower body (legs and abdomen) to the heart.

Intermittent Claudication — Pain, cramping or fatigue in the legs and buttocks that occurs during activity and subsides when a person stands still. It's caused by poor blood circulation in leg arteries due to buildups of plaque. It is a common, early symptom of peripheral artery disease (PAD). This condition may occur in both legs, and the symptoms often get worse over time. Smokers have a much greater risk for this condition. A program of daily walking for short periods, with intermittent stops when pain or cramping occur, may help improve the symptoms, but it is necessary to treat the underlying conditions,

Intern — A term for a physician in first-year training after medical school. The first year of a residency is typically called an internship.

Intraaortic Balloon Pump — A device used in treating severe left ventricular failure. The device essentially assists the left ventricle to pump and increases cardiac output. This helps relieve pulmonary congestion and heart failure.

Intravascular Ultrasound — A technique in which an ultrasound catheter is placed in the bloodstream during a heart catheterization to visualize blood vessels "from the inside." This technique is particularly helpful in cases of complex narrowing (stenosis), as may occur in the aorta (coarctation) or pulmonary arteries.

Invasive Procedure — A medical procedure in which the body is "invaded" or entered by a needle, tube, device or scope. Invasive procedures can include anything from the simple needle prick for a blood test or shot, to inserting a tube, device or scope, to major surgeries.

Ischemia — Reduced blood flow to an organ, usually due to a constricted or blocked artery.

Ischemic Heart Disease (Coronary Artery Disease, Coronary Heart Disease) — Blockages in the coronary arteries lead to ischemia, or decreased blood flow to the heart muscle. Decreased blood flow means decreased oxygen supply to the cells, and the body feels that as pain. When more oxygen is needed, as with exercise, the heart cannot meet the demands. When the heart suffers from a lack of oxygen, chest pain (angina) can occur.

Ischemic Stroke — The death of or injury to brain cells caused when a blood clot or other particle blocks an artery in the brain (cerebral artery) or leading to it, such as the carotid (neck) artery. Cerebral thrombosis and cerebral embolism are ischemic strokes.

J-Curve Phenomenon — When the blood pressure or blood cholesterol levels of large groups of people are plotted on a graph against risk of death from cardiovascular disease (CVD), it often results in a J-shaped curve. This curve shows that those with higher blood pressure and/or cholesterol levels, closer to tha top of the curve, are more likely to die from CVD. The curve also shows that those at the lowest end of the curve (with very low blood pressure and/or low cholesterol levels) also have higher CVD mortality. This accounts for the J shape and is known as the J-curve phenomenon. Most evidence, however, indicates that people at the bottom-left part of the curve (with very low blood pressure and low cholesterol levels) tend to be different from the general population in other ways. Those differences may contribute to the apparent increase in mortality.

Kawasaki Disease (Kawasaki Syndrome) — A rare, acute children's illness that involves inflammation of the blood vessels, particularly the coronary arteries, and the heart muscle (myocarditis) or the sac surrounding the heart (pericarditis). It is characterized by fever and swelling and can also cause red eyes, inflammation of the lips and mouth, swollen and red hands and feet, and swollen lymph nodes. The coronary arteries or other parts of the heart are affected in up to 20 percent of children with this disease. The cause has not been determined. (Also known as Mucocutaneous Lymph Node Syndrome.)

Laser Angioplasty — A technique used to open coronary arteries blocked by plaque. A catheter with a laser at its tip is inserted into an artery. Then it's advanced through the artery to the blockage. When the laser is in position, it emits pulsating beams of light that vaporize the plaque.

LDL Cholesterol (Low-Density Lipoprotein) — Often called "bad" cholesterol, LDL cholesterol is the major cholesterol carrier in the blood. If too much LDL cholesterol circulates in the blood, it can slowly build up in the walls of the arteries that lead to the heart and brain. Together with other substances it can form plaque, a thick, hard deposit that can clog those arteries. This condition is known as atherosclerosis. A high level of LDL cholesterol (160 mg/dL and above) reflects an increased risk of heart disease. An optimal level is less than 100 mg/dL. Levels from 100–129 mg/dL are near or optimal. Levels from 130–159 mg/dL are borderline high, which also increases risk for heart disease or stroke. LDL cholesterol level may be a better indicator of risk for a heart attack or stroke than total cholesterol, and drug therapy is initiated based on the level of LDL cholesterol. The lower the LDL cholesterol, the lower the risk for heart disease or stroke. For people with heart disease, the LDL cholesterol should be less than 100 mg/dL. For those with severe heart disease, the doctor may suggest that tha LDL cholesterol level be less than 70 mg/dL.

Left-sided Heart Failure (Left-ventricular Heart Failure) — Heart failure in which the left side of the heart must work harder to pump the same emount of blood. This type of heart failure usually causes breething difficulties.

Left-ventricular Assist Device (LVAD) — A battery-operated mechanical pump that is surgically implanted and is used to aid the natural pumping action of the heart's left ventricle. This device is sometimes called a "bridge to transplant" because it buys time until a heart trensplant can be performed.

Lipid — A fatty substance insoluble in blood. Cholesterol, cholesterol compounds, and triglycerides are all lipids. They are transported in the blood as part of large molecules called lipoproteins. Abnormalities in lipids can contribute to heart disease. It is recommended that all adufts age 20 or older have a fasting lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride) done every 5 years. People at higher risk for cardiovascular disease (CVD) or who are on cholesterol-lowering medication will need to have their cholesterol checked more often.

Lipid Testing — A "lipid panel" is taken when cholesterol levels in the blood are tested. Lipids are fats in the blood and include low-density lipoprotein cholesterol (LDL or "bad" cholesterol), high-density lipoprotein cholesterol (HDL or "good" cholesterol) and triglycerides. For the best results, blood should be drawn from a vein in the morning after fasting (nothing to eat or drink) for at least 12 hours. Another blood fat that may be tested is lipoprotein(a), or Lp(a). This is a genetic variation of plasma LDL. Lp(a) may interfere with the body's ability to dissolve blood clots and may play a role in the development of atherosclerosis (fatty buildups in artery walls). High levels of Lp(a) increase the risk for heart disease, heart attack and stroke. Lp(a) is usually checked in those with early-onset heart disease, with family members with early-onset heart disease or in those who have heart disease but don't have the typical risk factors, such as high blood pressure, high cholesterol, etc.

Lipoprotein — The combination of a lipid (fat) surrounded by a protein; the protein allows the fat to travel in the blood. Lipoproteins are characterized by their density: high-density lipoprotein (HDL), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL). Cholesterol, a building block of the outer layer of cells (cell membranes) is transported through the blood by lipoproteins.

Long QT Syndrome— A condition that affects the heart's electrical system and may cause fast, chaotic heartbeats. It can cause fainting, and in some cases cardiac arrest. The heart's electrical system normally functions by causing the atria (upper chambers) and then the ventricles (lower chambers) to contract. This pattern of normal electrical signals produces a normal ECG (EKG) with Q, R, S, and T waves. In long QT syndrome, the electrical signals are delayed because the electrical system cannot recharge fast enough to carry a signal. This condition increases the risk of a life-threatening arrhythmia known as ventricular tachycardia. People with long QT syndrome may have to limit physical activity, avoid certain medications or have an implantable cardioverter defibrillator (ICD) to prevent sudden death.

Low-Density Lipoprotein (LDL) — A type of protein that transports "bad" cholesterol in the blood. It's the major cholesterol carrier in the blood. (See **LDL Cholesterol.**)

Lp(a) Cholesterol — A genetic variation of LDL cholesterol. Lp(a) is a lipoprotein that resembles LDL in composition with an abnormal protein, termed (a), attached. It can interfere with the body's ability to dissolve blood clots. A high level of Lp(a) is an important risk factor for developing atherosclerosis prematurely. High levels of Lp(a) increase the risk for heart disease, heart attack and stroke. Lp (a) is usually checked in those with early-onset heart disease, with family members with early-onset heart disease or in those who have heart disease but who do not have the typical risk factors, such as high blood pressure, high cholesterol, etc.

Lumen — The open space within a tube, such as a blood vessel.

Magnetic Resonance Imaging (MRI), Nuclear Magnetic Resonance (NMR) Imaging — An imaging procedure that uses powerful magnets to look inside the body. Computer-generated pictures can image the heart muscle and evaluate various heart problems. It can outline the affected part of the brain and help define problems created by stroke. Coronary magnetic resonance angiography (CMRA) combines standard magnetic resonance (MR) imaging with an injection of a chemical dye, called a contrast medium. This allows visualization and precise measurement of blood flow to the heart muscle.

Maze Procedure — A surgical procedure to control atrial fibrillation and/or atrial flutter. A number of incisions are made in the atria to block the path of the arrhythmia.

Minimally Invasive Heart Surgery (MIHS), (Limited Access Coronary Artery Surgery) — An alternative to standard bypass surgery (CABG). Small incisions (ports) are made in the chest. Chest arteries or veins from the leg are attached to the heart to "bypass" the clogged coronary artery or arteries. The instruments are passed through the ports to perform the bypasses. In some cases the surgeon views these operations on video monitors rather than directly.

Mitral Valve — The valve located between the heart's left upper chamber (atrium) and left lower chamber (ventricle). It has two flaps (cusps) that open and close, similar to a double door.

Mitral Valve Prolapse (MVP) — In MVP, one or both valve flaps are enlarged, and some of their supporting "strings" may be too long. When the heart pumps (contracts), the mitral valve flaps don't close smoothly or evenly. Instead, part of one or both flaps collapses backward into the left atrium. This sometimes lets a small amount of blood leak backward through the valve. This may cause a heart murmur. (Also known as Click-Murmur Syndrome, Barlow's Syndrome, Balloon Mitral Valve and Floppy Valve Syndrome.)

Mitral Valve Stenosis — Stenosis literally means narrowing of an opening. Stenosis of the mitral valve limits the forward flow of blood from the heart's left upper chamber (atrium) to the left lower chamber (ventricle). This can cause a backup of blood and fluid in the lungs. Mitral valve stenosis most commonly develops many years after a person has had rheumatic fever, although many people diagnosed with the condition don't recall ever having the illness.

Monounsaturated Fats — A type of fat found in many oils (mostly canola, olive and peanut), nuts and avocados. These fats may help to lower blood cholesterol if used in place of saturated fats. However, mono-unsaturated fats have a lot of calories, so intake should be limited.

Mortality — The total number of deaths from a given disease in a population during an interval of time, usually a year.

Mucocutaneous Lymph Node Syndrome — **(See Kawasaki Disease)**

Myocardial Biopsy (Endomyocardial Biopsy) — In this test a small amount of tissue is removed from the internal lining of the heart for testing. It is used to help diagnose and treat heart muscle disorders and is also used to detect rejection of the new heart after a heart transplant. A long, flexible tube, called a catheter, is inserted into a vein and threaded up into the heart. The doctor can guide the catheter by watching its movement on a monitor showing an X-ray image of the area. The tip of the catheter is fitted with tiny jaws that the doctor can open and close. Once the catheter is in place, the doctor will take several small

snips of muscle for microscopic examination.

Myocardial Infarction — Medical term for heart attack. It is the damaging or death of an area of the heart muscle (myocardium) resulting from a blocked blood supply to that area.

Myocardial Ischemia — A condition in which there is not enough blood flow (and thus oxygen and nutrient supply) to the heart muscle.

Myocardial Perfusion Imaging (MPI) — (See **Thallium Stress Test**)

Myocarditis — Inflammation of the heart muscle (myocardium).

Myocardium — The muscular center layer of the heart between the outer layer (epicardium) and the inner layer (endocardium). The myocardium is responsible for the heart's pumping action and contracts to pump blood out of the heart and then relaxes as the heart refills with returning blood. The myocardium is the layer that has the largest oxygen needs and is most affected by decreased blood flow (ischemia).

Nitroglycerin — A drug (a vasodilator) that relaxes (dilates) blood vessels and increases the supply of blood and oxygen to the heart while reducing its workload. It's prescribed to patients who can't tolerate ACE inhibitors (another type of medicine that relaxes the blood vessels). "Nitro" is used to treat acute chest pain (angina), in which case it is prescribed as quick-dissolving pills to be placed under the tongue when needed. It can also be prescribed as a routine medication, in which case it is available as slower-release pills, creams or patches. When the blood vessels dilate, blood flow to the tissues increases. This can relieve chest pain.

Norwood Procedure — A complex surgical procedure used for hypoplastic left-heart syndrome (and similar variants) where reconstruction of the absent or small aorta is accomplished by using the patient's own pulmonary artery. This allows unobstructed blood flow to be delivered to the body. As part of the Norwood procedure, the wall between the heart's upper chambers (atria) is removed (atrial septectomy), and a small Gore-tex® tube (shunt) is inserted from the aorta to the pulmonary arteries.

Nurse Practitioner (NP) — An advanced practice nurse with special training and an advanced degree in nursing. Pediatric nurse practitioners (PNPs) may perform examinations, order medications and diagnostic procedures, educate staff and families and provide continuity of care between inpatient and outpatient settings.

Obesity — An excess of body fat. Obesity is defined as a body mass index (BMI) of 30.0 kg/m^2 or greater, or about 30 pounds or move over ideal body weight. Extreme obesity is defined as a BMI of 40.0 kg/m^2 or more. People who have too much fat, especially in the waist area, are at a higher risk for health problems including high blood pressure, high blood cholesterol, diabetes, heart disease and stroke.

Occluded Artery — An artery in which blood flow has been impaired (occluded) by a blockage.

Occlusion Devices (Atrial and Ventricular Septal Defect Occluders) — A number of investigators are designing devices that can be delivered through a catheter to close holes in the heart's upper chamber (ASDs) and lower chambers (VSDs). A number of these devices have been successfully used in recent clinical trials supervised by the Food and Drug Administration, but the follow-up is quite short at this time.

Open-Heart Surgery — (See **Coronary Bypass Surgery**)

Overweight — A body mass index (BMI) of 25.0–29.9 kg/m^2. A BMI of 25 kg/m^2 corresponds to about 10 percent over ideal body weight.

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Cardiac Glossary

A–C D–O P–Z

A B C D E F G H I J K L M N O P Q R S T U V W X Y Z

Click on the image to see a detailed medical illustration.

Pacemaker — The "natural" pacemaker of the heart is called the sinus node. It's a small group of specialized cells in the top of the heart's right chamber (atrium). It produces the electrical impulses that travel down to the heart's lower chambers (ventricles), causing the heart to contract. An "artificial pacemaker" is an electrical device that can substitute for a defective natural pacemaker or conduction pathway. An artificial pacemaker regulates the speed and rhythm of the heartbeat. Usually these devices are used for hearts that beat too slowly. Pacemakers run on batteries and usually last many years.

Palpitations — The sensation of the heart beating rapidly or irregularly.

Paramedical — Pertaining or closely related to the art or practice of medicine. This term is often applied to personnel whose work supports, or is closely related to, that of practicing physicians.

Patent Ductus Arteriosus (PDA) — A congenital heart defect that allows blood to mix between the pulmonary artery and the aorta. Before birth an open passageway (the ductus arteriosus) exists between these two blood vessels. Normally this closes within a few hours of birth. When this doesn't happen, some blood that should flow through the aorta and on to nourish the body returns to the lungs. A ductus that doesn't close is quite common in premature infants but rather rare in full-term babies. If the ductus arteriosus is large, a child may tire quickly, grow slowly, catch pneumonia easily and breathe rapidly. In some children symptoms may not occur until after the first weeks or months of life. If the ductus arteriosus is small, the child seems well. If surgery is needed, the surgeon can close the ductus arteriosus by tying it, without opening the heart. If there's no other defect, this restores the circulation to normal.

Percutaneous Transluminal Coronary Angioplasty (PTCA) — (See **Angioplasty**)

Perfusion — Blood flow.

Pericarditis — A disorder caused by inflammation of the pericardium, which is the sac-like covering of the heart. It's usually a complication of a viral, bacterial or fungal infection. It can also result from a heart attack, cancer, radiation treatment, injury or surgery. It most often affects men ages 20–50, but can also occur in children.

Pericardium — The outer fibrous "sac" that surrounds the heart.

Peripheral Artery Disease (PAD) — A type of peripheral vascular disease that affects blood circulation, mainly in arteries leading to the legs and feet. It's caused by atherosclerosis. Symptoms include pain in the legs or buttocks when exercising that goes away when the activity is stopped, though not everyone has symptoms. Smokers are at a much higher risk for PAD. It can be diagnosed with a quick, painless test called an ankle-brachial index (ABI) test. Since it often goes undiagnosed, it's important to ask a healthcare professional to administer the test if you have symptoms or smoke. **Peripheral Vascular Disease** — Diseases of blood vessels outside the heart and brain or diseases of the lymph vessels.

Often it's a narrowing of vessels carrying blood to leg and arm muscles. Peripheral artery disease (PAD) is a common form of peripheral vascular disease.

Phlebotomy — Removing blood from the vein. This term applies to routine laboratory blood tests, but in patients with high blood counts (see **Polycythemia**), a larger amount of blood is removed and replaced with intravenous fluid to lower the blood count.

Phospholipid — A type of fat (lipid) that contains phosphorous. It splits into fatty acids, glycerin and a nitrogen compound when water is added.

Plaque — Also called atheroma, this is a cholesterol-laden buildup in the interior wall of blood vessels. After years it may become calcified and hard. It may also rupture. If this happens, a blood clot may form on the plaque and block blood flow, potentially causing a heart attack or stroke. The building up of plaque and hardening of the arteries is known as atherosclerosis.

Plasma Lipid — The lipid (fatty particles) carried in blood.

Platelets — An element in blood that aids in blood clotting.

Polycythemia — An elevated number of red blood cells, also referred to as a "high hematocrit" or "thick blood." Polycythemia is often seen in patients with lower-than-normal levels of oxygen in the blood.

Polyunsaturated Fats — A type of fat found mainly in vegetable oils such as corn, safflower, sunflower and soybean oils. They're usually liquid at room temperature. They may help lower blood cholesterol level when used in place of saturated fats.

Potassium (K+) — One of the electrolyte substances found naturally in the body that, together with sodium and calcium, regulates the body's water balance, maintains normal heart rhythm and is responsible for nerve impulse conduction and muscle contraction. A proper balance of potassium, sodium, calcium and magnesium is essential for normal excitability of muscle tissue, especially cardiac muscle, and plays a role in nerve conduction. Potassium levels are mainly controlled by the steroid hormone aldosterone, which causes the body to rid itself of excess potassium. Small changes in the potassium concentration outside cells can have substantial effects on the activity of nerves and muscles. This is particularly true of heart muscle. Low levels of potassium cause increased activity, which can lead to an irregular heartbeat (arrhythmia). High levels cause decreased activity. Either situation can lead to cardiac arrest in some circumstances.

Premature Atrial Contraction (PAC) — An early beat of the heart's upper chamber (atrium) that may feel like the heart "skipped" a beat. (See also **Palpitations**.)

Premature Ventricular Contraction (PVC) — An early beat of the heart's lower chamber (ventricle) that may feel like the heart "skipped" a beat. (See also **Palpitations**.)

Prevalence — The total number of cases of a given disease in a population at a specific time. Prevalence is sometimes expressed as a percentage of population.

Primary Care Doctor — A general internist or family physician who provides patients with routine preventive health care and is their first contact when medical problems arise.

Progestin — Any of a group of steroid hormones that have the effect of the female hormone progesterone. Used in oral contraceptives and hormone replacement therapy. There is also a natural form of progestin.

Prophylaxis — Preventive treatment.

Prostaglandins — One of a number of hormone-like substances that participate in a wide range of body functions such as the contraction and relaxation of smooth muscle, the dilation and constriction of blood vessels, control of blood pressure and modulation of inflammation. Prostaglandins are derived from a

chemical called arachidonic acid.

Pulmonary — Pertaining to the lungs.

Pulmonary Artery Catheterization (Right Heart Catheterization) — Used to evaluate primary pulmonary hypertension. In this procedure the doctor places a thin, flexible tube (called a Swan-Ganz catheter) through an artery or vein in the patient's arm, leg or neck and then threads it into the right ventricle and pulmonary artery. This is a common way to measure the pressure in the pulmonary artery and find out what treatment is appropriate for a given patient. It is also used in critically ill patients to provide continuous monitoring of heart function. (Sometimes called Swan-Ganz Catheterization)

Pulmonary Atresia — A congenital heart defect in which no pulmonary valve exists. Blood can't flow from the right ventricle into the pulmonary artery and on to the lungs. This results is a blue discoloration of the skin (cyanosis).

Pulmonary Edema — Fluid buildup (edema) in the lungs usually due to mitral stenosis or left ventricular failure. Symptoms of pulmonary edema include difficulty breathing, coughing up blood, excessive sweating, anxiety and pale skin.

Pulmonary Stenosis (PS) — A congenital heart defect in which the pulmonary or pulmonic valve is defective and doesn't open properly. The pulmonary valve is between the right ventricle and the pulmonary artery. It opens to allow blood to flow from the right ventricle to the lungs. This forces the right ventricle to pump harder than normal to overcome the obstruction. Treatment is needed when the pressure in the right ventricle is higher than normal. In most children the obstruction can be relieved by a procedure called balloon valvuloplasty. Others may need open-heart surgery. People with pulmonary stenosis, before and after treatment, are at risk for getting an infection of the valve (endocarditis).

Pulmonary Veins — Four veins that return blood from the lungs to the heart. They empty into the left upper chamber (atrium) of the heart.

Pulmonic (Pulmonary) Valve — The heart valve between the right ventricle and the pulmonary artery. It has three flaps (cusps).

Reentry — A type of abnormal conduction in which electrical impulses get caught in a merry-go-round-like sequence. This is a common cause of tachycardias.

Regurgitation — The leakage that results when a heart valve that doesn't close properly lets blood leak back into the chamber from which it was pumped.

Reperfusion Therapy — One or more techniques to restore blood flow to part of the heart muscle damaged during a heart attack, or part of the brain injured during a stroke. It may include clot-dissolving drugs (thrombolysis), balloon angioplasty or surgery.

Resident — A licensed physician completing training in a primary specialty (e.g., pediatrics, surgery, internal medicine, obstetrics/gynecology, etc.) after medical school.

Restenosis — A renarrowing of an artery after angioplasty, stent or bypass surgery. About one-third of patients who undergo PTCA (percutaneous transluminal coronary angioplasty) have restenosis of the widened segment within about six months of the procedure. Restenosed arteries may have to undergo another angioplasty. Research is now investigating ways to prevent restenosis. Restenosis may also occur in valves after balloon valvuloplasty.

Rheumatic Heart Disease — Damage done to the heart, particularly the heart valves, by one or more attacks of rheumatic fever.

Right Heart Ventriculography — A study of the right chambers (atrium and ventricle) of the heart. This test is used to obtain measurements of pressure, oxygen and cardiac output through a thin flexible tube called a catheter. Occasionally, visualizing the right chambers is also necessary. This is done by injecting contrast media (dye) through the catheter into the heart's right side with a rapid succession of X-rays taken to capture images of blood flow. Right-heart angiography is performed to detect abnormalities in blood flow through the heart's

right side.

Right-Sided Heart Failure (Right Ventricular Heart Failure) — Heart failure caused by damage to the heart's right-sided chambers. This usually occurs as a result of left-sided heart failure. When the left ventricle fails, increased fluid pressure is, in effect, transferred back through the lungs, ultimately damaging the heart's right side. When the right side loses pumping power, blood backs up in the body's veins. This usually causes swelling in the legs and ankles.

Risk Factor — An element or condition involving certain hazard or danger. When referring to the heart and blood vessels, a *positive* risk factor is associated with an *increased* chance of developing cardiovascular disease including stroke. A *negative* risk factor is associated with a *reduced* chance of developing heart and blood vessel disease.

Rubella — Commonly known as German measles.

Saturated Fats — Types of fat found in all foods from animals (i.e., butter, cheese, whole milk, ice cream, cream and fatty meats) and from some plants (i.e., coconut, palm and palm kernel oils). They are the biggest dietary cause of high LDL "bad" cholesterol levels. Limit any foods that are high (for example, over 20 percent) in saturated fat. Limit saturated fat intake to 7–10 percent of total calories (or less) each day. The recommendation for people with coronary heart disease or an LDL cholesterol level of 100 mg/dL or greater is 25–35 percent of calories from fat per day, with *less* than 7 percent coming from saturated fat.

Septum — The muscular wall dividing the chambers on tha heart's left side from the chambers on the right.

Shunt — (1) An abnormal flow pattern of blood through the chambers of the heart or through the large arteries leaving the heart. A "left-to-right" shunt results in extra blood flow entering the lungs, while a "right-to-left" shunt results in decreased blood flow to the lungs, low oxygen levels and cyanosis. (2) A surgically created connection designed to increase the delivery of blood to the lungs. Shunts are also used in bypass surgery and to drain fluids from the body. The most common types of these shunts are named for the physicians who popularized them (Blalock-Taussig, Waterston, Potts, Glenn). A "modified" shunt may involve the use of artificial material, such as Gore-tex®.

Sickle Cell Anemia — A genetic blood disorder that mainly affects African Americans. "Sickled" red blood cells are less able to carry oxygen to the body's tissues and organs. They also tend to stick to blood vessel walls. This can block arteries to the brain and cause a stroke.

Side Effect — An undesired reaction that results from a medication or therapy. For example, heart failure medications can cause side effects such as headaches, nausea, dizziness, kidney complications and low blood pressure.

Silent Ischemia — Episodes of ischemia that aran't accompanied by pain.

Single Photon Emission Computed Tomography (SPECT) — A nuclear imaging technique that involves injecting a radioactive liquid into the blood, then taking a series of pictures around the chest. SPECT is used to examine blood flow in the heart and to determine how well the heart is pumping. It is also used to diagnose coronary artery disease (CAD).

Sinoatrial (SA) or Sinus Node — Called the "natural pacemaker" of the heart, the SA is located in the right atrium (upper chamber) of the heart. It initiates the heart's electrical activity, stimulating muscle contraction, which pumps blood to the body. (See **Pacemaker**)

Sinus Rhythm — The normal heart rate and rhythm of the heart. The heart rate during normal sinus rhythm is 60 to 100 beats per minute (BPM).

Social Worker — Within the hospital setting, a person specially trained to counsel and assist in the emotional, social, environmental and financial needs of the heart patient and family. This person often interacts as a liaison of need, working closely with medicel staff and the family, both during and after hospitalization.

Sodium (Na) — A mineral that, together with potassium and calcium, regulates the body's water balance, maintains normal heart rhythm and is responsible for nerve impulse conduction and muscle contraction. In general, the more sodium consumed, the more water is retained in the body. Excessive intake of sodium from food contributes to high blood pressure in some people. In people who already have high blood pressure, too much sodium may increase the risk of stroke, heart disease and kidney damage. Table salt (sodium chloride) is nearly half sodium. The recommended daily intake of sodium is less than 2300 mg, or slightly less than one teaspoon.

Spasm — The sudden, temporary or prolonged contraction of a muscle or artery.

Sphygmomanometer (Blood Pressure Monitor) — An instrument for measuring blood pressure.

Stable Angina — Predictable chest discomfort that usually occurs during exertion (such as running to catch a bus) or under mental or emotional stress. Normally the chest discomfort is relieved with rest, nitroglycerin or both.

Stages of Heart Failure — Developed by the American Heart Association and American College of Cardiology in 2001, this staging system is designed to evaluate the development and progression of heart failure. Stages A and B represent people who have not yet developed heart failure, but are at high risk to do so because of coronary artery disease (CAD), high blood pressure, diabetes or other predisposing risk factor. Stage C includes patients with past or current symptoms of heart failure who have structural heart disease. Stage D includes patients who have advanced heart failure that is difficult to manage with standard treatment.

Statins — A group of drugs used to reduce elevated low-density lipoprotein (LDL) or "bad" cholesterol, which is associated with increased risk of cardiovascular disease. They work in the liver to prevent cholesterol from forming. They are also known as HMG CoA reductase inhibitors.

Stenosis — The narrowing or constriction of an opening, such as a blood vessel or heart valve.

Stent Procedure — Using a wire mesh tube (a stent) to prop open an artery that's recently been cleared using angioplasty.

Stethoscope — An instrument for listening to sounds within the body.

"Strep" Infection (Streptococcal Infection) — An infection, usually in the throat, resulting from streptococcus bacteria.

Stress — Bodily or mental tension resulting from a person's response to physical, chemical or emotional factors. Stress can refer to physical exertion as well as mental anxiety.

Stress Test — (See **Exercise Stress Test**)

Stroke (Apoplexy, Cerebrovascular Accident) — An interruption of blood flow to the brain causing paralysis, slurred speech and/or altered brain function. It may be caused by a blood clot blocking circulation or by bleeding into brain tissue causing tissue damage. A stroke can happen when a blood vessel carrying blood to the brain is blocked by a blood clot. This is called an *ischemic stroke*. A hemorrhagic stroke occurs when a blood vessel breaks open due to trauma or an aneurysm ruptures causing blood to leak into the brain.

Subaortic Stenosis — A congenital heart defect in which the left ventricle is narrowed (stenosis) just below the aortic valve, which blood passes through to go into the aorta. This limits the flow of blood out of the left ventricle. The defect can also be due to a form of cardiomyopathy. Treatment depends on the cause and severity of the narrowing and includes drugs and surgery. People with subaortic stenosis, before and after treatment, are at risk for infection within the aorta or the heart valves (endocarditis). To help prevent this, they should take antibiotics before certain dental and surgical procedures.

Subarachnoid Hemorrhage — Bleeding from a blood vessel on the surface of the brain into the space between the brain and the skull. A type of stroke.

Sudden Cardiac Death (SCD, Sudden Death) — SCD is death resulting from the abrupt loss of heart function (cardiac arrest). Death occurs within minutes after the heart stops. SCD due to cardiac arrest may be prevented if CPR (cardiopulmonary resuscitation) is performed and a defibrillator is used to shock the heart and restore a normal heart rhythm within a few minutes. Most of the cardiac arrests that lead to sudden death occur when the electrical impulses in the diseased heart become rapid (ventricular tachycardia) or chaotic (ventricular fibrillation) or both. A heart attack may cause cardiac arrest and sudden cardiac death, but the terms aren't synonymous

Superior Vena Cava — A major vein that carries blood from the upper body (head, neck, chest and arms) to the heart.

Supraventricular Tachycardia — A condition in which heart tissue in either the upper chambers (atria) or the middle region (above the ventricles) develops pacemaker activity, resulting in an abnormally fast heartbeat.

Swan-Ganz Catheter — A soft catheter with an expandable balloon tip that is used for measuring blood pressure in the pulmonary artery, named for its inventors, Jeremy Swan and William Ganz. (See **Pulmonary Artery Catheterization**)

Sympathetic Nerve Inhibitors — A class of antihypertensive drugs that reduce blood pressure by inhibiting the sympathetic nerves from constricting blood vessels.

 **Syncope** — Passing out, loss of consciousness or fainting caused by a temporary deficiency of oxygen in the brain.

Systole — The contraction phase of the normal heart cycle during which blood is driven into the aorta and pulmonary artery.

 **Systolic Blood Pressure** — The highest blood pressure measured in the arteries. The pressure of blood inside arteries that occurs during the pumping phase of the heartbeat. It is measured in millimeters of mercury (mmHg) and is the upper number in the standard blood pressure reading.

Systolic Heart Failure — A condition in which the heart pumps with less strength than normal (decreased ejection fraction). As time goes on, the pumping chambers (ventricles) become thin, large and floppy. Because blood cannot be pumped out as well, it backs up into organs. This causes swelling (edema) (particularly noticed in the feet and ankles) and congestion in the lungs. As the disease progresses, the heart is unable to pump enough blood (and oxygen) around the body to meet its needs. This type of heart failure is more common and caused by conditions such as coronary artery disease (CAD), high blood pressure, valvular heart disease and idiopathic cardiomyopathy.

Tachycardia — An abnormally fast heartbeat (more than 100 beats per minute).

Tetralogy of Fallot — A complex, congenital heart defect with four components: ventricular septal defect, pulmonary valve stenosis, muscular right ventricle and the aorta directly over the ventricular septal defect. Blood pumped to the body contains less-than-normal amounts of oxygen. This results in cyanosis, a blue discoloration of the skin. Some infants with severe Tetralogy of Fallot may need an operation to give temporary relief by increasing blood flow to the lungs with a shunt. Most children with this condition have open-heart surgery before school age. After surgery the long-term outlook varies, depending largely on how severe the defects were before surgery. Lifelong medical follow-up is needed. People with Tetralogy of Fallot, before and after treatment, are at risk for getting an infection within the aorta or the heart valves (endocarditis). It's recommended that all people with uncorrected or partly corrected tetralogy of Fallot take antibiotics before certain dental procedures. If you (or your child) have had corrective surgery, ask your cardiologist whether these routine antibiotics are still needed.

 **Thallium Stress Test** — A type of nuclear scanning test similar to a routine

exercise stress test but with images. This test shows how well the heart muscle is supplied (perfused) with blood. It uses a radioactive substance called thallium that's injected into the bloodstream when the patient is at maximum level of exercise. Then pictures are taken of the heart's muscle cells using a special (gamma) camera. Patients who cannot physically exercise will receive a medication to increase blood flow in the heart as if they were exercising. The radionuclide tracers cardiolite and myoview can also be used instead of thallium for this test. (Also known as Myocardial Perfusion Imaging (MPI), Radionuclide Stress Test and Nuclear Stress Test.)

Thoracoscopic Surgery — Similar to arthroscopic surgery for joint surgery or laparoscopic surgery in the abdomen, thoracoscopic surgery is performed by using small incisions and video cameras to do procedures typically done through larger open incisions.

Three-dimensional ("3-D") Echocardiography — Current echo technology allows the echo to be viewed in only two dimensions. Three-dimensional echocardiography allows the physician to "reconstruct" the heart and view the structural defects at any angle.

Thrombolysis — The breaking up of a blood clot.

Thrombosis — The formation or presence of a blood clot (thrombus) inside a blood vessel or chamber of the heart.

Thrombus — A blood clot that forms inside a blood vessel or chamber of the heart.

Tissue Plasminogen Activator (tPA) — One of several clot-dissolving (thrombolytic) drugs used during a heart attack or stroke to restore blood flow in a blocked artery. To be effective, it must be given within a few hours after symptoms begin. For a person having an acute heart attack, tPA works by dissolving a major clot quickly. By dissolving the clot, the blood is able to start flowing again to that area of the heart. If the blood flow to the heart is started again rapidly, it may prevent long-term damage to the heart muscle and may even stop an event that could have been fatal.

Total Anomalous Pulmonary Venous Connection (Total Anomalous Pulmonary Venous Return TAPVR) — A congenital heart defect in which the pulmonary veins bring oxygenated (red) blood from the lungs back to the right side of the heart rather than the left side of the heart where it should be. The blood passing through the aorta to the body doesn't have enough oxygen, which causes the child to look blue (cyanotic). This condition requires surgical correction, the timing of which depends on how sick the patient is. The surgery may be done in the newborn period if the infant has severe systems or at some time during the first six months of life. It is an open-heart procedure.

Trans Fats (Trans Fatty Acids) — A fat that is formed when liquid vegetable oils go through a chemical process called hydrogenation in which hydrogen is added to make the oils more solid. Hydrogenated vegetable fats are used by food processors because they allow longer shelf life and give food desirable taste, shape and texture. The majority of trans fat can be found in shortenings, stick (or hard) margarine, cookies, crackers, snack foods, fried foods (including fried fast food), doughnuts, pastries, baked goods and other processed foods made with or fried in partially hydrogenated oils. Some trans fat is found naturally in small amounts in various meat and dairy products. Evidence suggests that consuming trans fat can raise LDL ("bad) cholesterol levels and lower HDL ("good") cholesterol levels.

Transesophageal Echocardiography (TEE) — An ultrasound technique in which the ultrasound probe (about as large as a pinky finger) is placed in the esophagus to "look" at the heart from behind. Transesophageal echocardiography is much more sensitive than transthoracic (across the chest) echocardiography, as overlying structures (bone and lungs) do not obscure the view. This technique requires sedation in almost all cases.

Transient Ischemic Attack (TIA) — Known as a "mini stroke", TIA is caused by a temporary disturbance of blood supply to an area of the brain. It lasts for only for a short time. TIA is an extremely important indicator of future stroke. The age of

onset varies, but incidence rises dramatically after age 50. TIA is more common among men and African Americans. Also called a "little stroke".

Transmyocardial Revascularization (TMR) — A procedure used to relieve severe angina or chest pain in very ill patients who aren't candidates for bypass surgery or angioplasty. In this procedure, a surgeon makes an incision on the left breast to expose the heart. Then, using a laser, the surgeon drills a series of holes (20 to 40 mm wide) from the outside of the heart into the haart's pumping chamber. In some patients TMR is combined with bypass surgery. How TMR reduces angina still isn't fully understood. The laser may stimulate new blood vessels to grow, called angiogenesis, or it may destroy nerve fibers to the heart, making patients unable to feel their chest pain.

Transposition of the Great Arteries — A congenital heart defect in which the positions of the pulmonary artery and the aorta are reversed. The aorta receives the oxygen-poor blood from the right ventricle, but it's carried back to the body without receiving more oxygen. Likewise, the pulmonary artery receives the oxygen-rich blood from the left ventricle but carries it back to the lungs. Most babies with transposition of the great arteries are extremely blue (cyanotic) soon after birth. Two general types of surgery may be used to help fix the transposition, but the long-term outlook depends largely on how severe the defects were before surgery. Lifelong follow-up is needed. People with transposition of the great arteries, before and after treatment, are at risk for getting an infection on the heart's walls or valves (endocarditis). It's recommended that all people with uncorrected or partly corrected transposition of the great arteries take antibiotics before certain dental procedures. If you (or your child) have had corrective surgery, ask your cardiologist whether these routine antibiotics are still needed.

Tricuspid Atresia — A congenital heart defect in which there's no tricuspid valve. That means no blood can flow from the right atrium to the right ventricle. As a result, the right ventricle is small and not fully developed. Often a surgical shunting procedure is needed to increase blood flow to the lungs. Some children with tricuspid atresia have too much blood flowing to the lungs. They may need a procedure (pulmonary artery banding) to reduce blood flow to the lungs. Other children with tricuspid atresia may have a more functional repair (Fontan procedure) in which a connection is created between the right atrium and pulmonary artery, and the atrial defect is closed. Children with tricuspid atresia require lifelong follow-up by a cardiologist. People with tricuspid atresia, before and after treatment, are at risk for getting an infection of the valves (endocarditis). It's recommended that all people with uncorrected or partially corrected tricuspid atresia take antibiotics before certain dental procedures. If you (or your child) has had corrective surgery, ask your cardiologist whether these routine antibiotics are still needed.

Tricuspid Valve — The heart valve between the right atrium and the right ventricle. It has three flaps (cusps).

Triglyceride — Triglycerides are the chemical form in which most fat exists in food as well as in the body. They're also present in blood plasma and, in association with cholesterol, form the plasma lipids. They can be made in the body from energy sources such as carbohydrates or come from fats eaten in foods. Calories ingested in a meal and not used immediately by tissues are converted to triglycerides and transported to fat cells to be stored. Hormones regulate the release of triglycerides from fat tissue so they meet the body's needs for energy between meals. The normal level of triglycerides is less than 150 mg/dL. Excess triglycerides has been linked to the occurrence of coronary artery disease (CAD).

Troponins — Proteins found in heart muscle. Blood tests for troponins can detect heart muscle injury.

Truncus Arteriosus — A complex congenital heart defect where only one artery arises from the heart and forms the aorta and pulmonary artery. Surgery for this condition usually is required early in life. Children with truncus arteriosus need lifelong follow-up to see how well the heart is working. People with truncus arteriosus, before and after treatment, are at risk for getting an infection on the heart's walls or valves (endocarditis). It is recommended that all people with uncorrected or partially corrected tricuspid atresia take antibiotics before certain dental procedures. If you (or your child) has had corrective surgery, ask your cardiologist whether there is still a need for these routine antibiotics.

Ultrafast®CT — (See **Electron-Beam Computed Tomography**)

Ultrasound — High-frequency sound vibrations, not audible to the human ear, used in medical diagnosis.

Unstable Angina — Chest pain or discomfort that's unexpected and usually occurs while at rest. The discomfort may be more severe and prolonged than typical angina or be the first time a person has angina. Unstable angina is an acute coronary syndrome and should be treated as an emergency.

Vaccine — Weakened or dead germs, given by injection, that protect against infectious disease. People with heart failure should receive a yearly influenza vaccine and a one-time pneumococcal vaccine (to guard against pneumonia).

Variant Angina Pectoris (or Prinzmetal's Angina) — Attacks of chest pain due to coronary artery spasm that occur almost exclusively when a person is at rest.

Vascular — Pertaining to blood vessels.

Vasoconstriction — A narrowing of a blood vessel, causing decreased blood flow to a part of the body.

Vasodilators — A group of drugs that cause the muscle in the walls of the blood vessels (especially the arterioles) to relax, allowing the vessels to dilate. Nitroglycerin tablets are a form of vasodilator.

Vein — One of a series of vessels that carries blood from various parts of the body back to the heart.

Ventricle — One of the two lower chambers of the heart that receive blood from the atria (upper chambers). The right ventricle pumps blood to the lungs and the left ventricle pumps blood to the rest of the body.

Ventricular Fibrillation (VF) — A severely abnormal heart rhythm (arrhythmia) that, unless treated immediately, causes death. During VF, the ventricles contract independently of the atria and in a disorganized manner. The most common cause of VF is a heart attack, but VF can occur whenever the heart muscle is affected by a poor supply of oxygen (ischemia) or by specific heart disorders. Other conditions that can lead to VF include congenital heart disease, heart surgery, heart muscle disease, electrocution or accidents involving direct trauma to the heart. VF is the main cause of sudden cardiac death (SCD). While many VF patients have no previous history of heart disease, they do have risk factors for cardiovascular disease, such as smoking, hypertension and diabetes.

Ventricular Septal Defect (VSD) — A congenital heart defect in which one or more holes exist in the muscular wall that separates the heart's right and left ventricles (lower chambers). It is the most common congenital heart defect. As with most types of congenital heart disease, no one knows what causes VSDs. This defect often occurs along with other congenital heart malformations. In adults, VSD is a rare but serious complication of heart attacks. These holes are related to the heart attack and do not result from a birth defect.

Ventricular Tachycardia — A very fast, abnormal heartbeat (arrhythmia) initiated within the heart's lower chambers (ventricles). VT is potentially lethal if the heart becomes unable to pump adequate blood through the body. VT can occur in the absence of apparent heart disease. It can also develop as a complication of a heart attack, following heart disease, surgery or with cardiomyopathy, valvular heart disease or myocarditis. Healed scar tissue from heart attacks can lead to VT days, months or years after the heart attack. VT can also result from anti-arrhythmic medications or from altered blood chemistries (such as a low potassium level), pH (acid-base) changes or insufficient oxygenation. VT is classified as nonsustained (often defined as lasting less than 30 seconds) or sustained. "Torsade de pointes" is a form of VT with a specific variation in the conduction of the ventricular stimulus.

Venules — Small veins, the blood vessels that carry blood back to the heart and lungs.

Vertebral Artery — One type of major blood vessel in the neck carrying blood

from the heart to the brain. The other type is carotid artery.

Wolff-Parkinson White Syndrome (WPW) — A condition in which the heart beats too fast due to abnormal, extra electrical pathways between the heart's upper and lower chambers. In a normal heart, the electrical signal moves from the heart's upper chambers (the atria) to the lower chambers (the ventricles), causing the heart to beat. If there's an extra conduction pathway, the electrical signal may cause a rapid heart rate (tachycardia). WPW can be present at birth (congenital), but symptoms can appear at any time. More women than men are diagnosed with WPW. Treatments include medications and some surgical procedures.

EXHIBIT 44

Glossary of Clinical Trials Terms

The following glossary was prepared to help the consumer become familiar with many of the common terms used in clinical trials.

ADVERSE REACTION: (Adverse Event.) An unwanted effect caused by the administration of drugs. Onset may be sudden or develop over time (See **Side Effects**).

ADVOCACY AND SUPPORT GROUPS: Organizations and groups that actively support participants and their families with valuable resources, including self-empowerment and survival tools.

APPROVED DRUGS: In the U.S., the Food and Drug Administration (FDA) must approve a substance as a drug before it can be marketed. The approval process involves several steps including pre-clinical laboratory and animal studies, clinical trials for safety and efficacy, filing of a New Drug Application by the manufacturer of the drug, FDA review of the application, and FDA approval/rejection of application (See **Food and Drug Administration**).

ARM: Any of the treatment groups in a randomized trial. Most randomized trials have two "arms," but some have three "arms," or even more (See **Randomized Trial**).

BASELINE: 1. Information gathered at the beginning of a study from which variations found in the study are measured. 2. A known value or quantity with which an unknown is compared when measured or assessed. 3. The initial time point in a clinical trial, just before a participant starts to receive the experimental treatment which is being tested. At this reference point, measurable values such as CD4 count are recorded. Safety and efficacy of a drug are often determined by monitoring changes from the baseline values.

BIAS: When a point of view prevents impartial judgment on issues relating to the subject of that point of view. In clinical studies, bias is controlled by blinding and randomization (See **Blind** and **Randomization**).

BLIND: A randomized trial is "Blind" if the participant is not told which arm of the trial he is on. A clinical trial is "Blind" if participants are unaware on whether they are in the experimental or control arm of the study; also called masked. (See **Single Blind Study** and **Double Blind Study**).

CLINICAL: Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science.

CLINICAL ENDPOINT: See **Endpoint**.

CLINICAL INVESTIGATOR: A medical researcher in charge of carrying out a clinical trial's protocol.

CLINICAL TRIAL: A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed. (See **Phase I**, **II**, **III**, and **IV Trials**).

COHORT: In epidemiology, a group of individuals with some characteristics in common.

COMMUNITY-BASED CLINICAL TRIAL (CBCT): A clinical trial conducted primarily through primary-care physicians rather than academic research facilities.

COMPASSIONATE USE: A method of providing experimental therapeutics prior to final FDA approval for use in humans. This procedure is used with very sick individuals who have no other treatment options. Often, case-by-case approval must be obtained from the FDA for "compassionate use" of a drug or therapy.

COMPLEMENTARY AND ALTERNATIVE THERAPY: Broad range of healing philosophies, approaches, and therapies that Western (conventional) medicine does not commonly use to promote well-being or treat health conditions. Examples include acupuncture, herbs, etc. Internet Address: http://www.nccam.nih.gov.

COMPLETED: See Recruitment Status

CONFIDENTIALITY REGARDING TRIAL PARTICIPANTS: Refers to maintaining the confidentiality of trial participants including their personal identity and all personal medical information. The trial participants' consent to the use of records for data verification purposes should be obtained prior to the trial and assurance must be given that confidentiality will be maintained.

CONTRAINDICATION: A specific circumstance when the use of certain treatments could be harmful.

CONTROL: A control is the nature of the intervention control.

CONTROL GROUP: The standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo (See Placebo and Standard Treatment).

CONTROLLED TRIALS: Control is a standard against which experimental observations may be evaluated. In clinical trials, one group of participants is given an experimental drug, while another group (i.e., the control group) is given either a standard treatment for the disease or a placebo.

DATA SAFETY AND MONITORING BOARD (DSMB): An independent committee, composed of community representatives and clinical research experts, that reviews data while a clinical trial is in progress to ensure that participants are not exposed to undue risk. A DSMB may recommend that a trial be stopped if there are safety concerns or if the trial objectives have been achieved.

DIAGNOSTIC TRIALS: Refers to trials that are are conducted to find better tests or procedures for diagnosing a particular disease or condition. Diagnostic trials usually include people who have signs or symptoms of the disease or condition being studied.

DOSE-RANGING STUDY: A clinical trial in which two or more doses of an agent (such as a drug) are tested against each other to determine which dose works best and is least harmful.

DOUBLE-BLIND STUDY: A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study. See Blinded Study, Single-Blind Study, and Placebo.

DOUBLE-MASKED STUDY: See Double-Blind Study.

DRUG-DRUG INTERACTION: A modification of the effect of a drug when administered with another drug. The effect may be an increase or a decrease in the action of either substance, or it may be an adverse effect that is not normally associated with either drug.

DSMB: See Data Safety and Monitoring Board.

EFFICACY: (Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the procedure mandated by the FDA, Phase II clinical trials gauge efficacy, and Phase III trials confirm it (See Food and Drug Administration (FDA), Phase II and III Trials).

ELIGIBILITY CRITERIA: Summary criteria for participant selection; includes Inclusion and Exclusion criteria. (See **Inclusion/Exclusion Criteria**)

EMPIRICAL: Based on experimental data, not on a theory.

ENDPOINT: Overall outcome that the protocol is designed to evaluate. Common endpoints are severe toxicity, disease progression, or death.

ENROLLING: The act of signing up participants into a study. Generally this process involves evaluating a participant with respect to the eligibility criteria of the study and going through the **informed consent** process.

EPIDEMIOLOGY: The branch of medical science that deals with the study of incidence and distribution and control of a disease in a population.

EXCLUSION/INCLUSION CRITERIA: See **Inclusion/Exclusion Criteria**.

EXPANDED ACCESS: Refers to any of the FDA procedures, such as compassionate use, parallel track, and treatment IND that distribute experimental drugs to participants who are failing on currently available treatments for their condition and also are unable to participate in ongoing clinical trials.

EXPERIMENTAL DRUG: A drug that is not FDA licensed for use in humans, or as a treatment for a particular condition (See **Off-Label Use**).

FDA: See **Food and Drug Administration**.

FOOD AND DRUG ADMINISTRATION (FDA): The U.S. Department of Health and Human Services agency responsible for ensuring the safety and effectiveness of all drugs, biologics, vaccines, and medical devices, including those used in the diagnosis, treatment, and prevention of HIV infection, AIDS, and AIDS-related opportunistic infections. The FDA also works with the blood banking industry to safeguard the nation's blood supply. Internet address: **http://www.fda.gov/**.

HYPOTHESIS: A supposition or assumption advanced as a basis for reasoning or argument, or as a guide to experimental investigation.

INCLUSION/EXCLUSION CRITERIA: The medical or social standards determining whether a person may or may not be allowed to enter a clinical trial. These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. It is important to note that inclusion and exclusion criteria are not used to reject people personally, but rather to identify appropriate participants and keep them safe.

IND: See **Investigational New Drug**.

INFORMED CONSENT: The process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study.

INFORMED CONSENT DOCUMENT: A document that describes the rights of the study participants, and includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

INSTITUTIONAL REVIEW BOARD (IRB): 1. A committee of physicians, statisticians, researchers, community advocates, and others that ensures that a clinical trial is ethical and that the rights of study participants are protected. All clinical trials in the U.S. must be approved by an IRB before they begin. 2. Every institution that conducts or supports biomedical or behavioral research involving human participants must, by federal regulation, have an IRB that initially approves and periodically reviews the research in order to protect the rights of human participants.

INTENT TO TREAT: Analysis of clinical trial results that includes all data from participants in the groups to which they were randomized (See **Randomization**) even if they never received the treatment.

INTERVENTION NAME: The generic name of the precise intervention being studied.

INTERVENTIONS: Primary interventions being studied: types of interventions are Drug, Gene Transfer, Vaccine, Behavior, Device, or Procedure.

INVESTIGATIONAL NEW DRUG: A new drug, antibiotic drug, or biological drug that is used in a clinical investigation. It also includes a biological product used *in vitro* for diagnostic purposes.

IRB: See **Institutional Review Board**.

MASKED: The knowledge of intervention assignment. See **Blind**

NATURAL HISTORY STUDY: Study of the natural development of something (such as an organism or a disease) over a period of time.

NEW DRUG APPLICATION (NDA): An application submitted by the manufacturer of a drug to the FDA - after clinical trials have been completed - for a license to market the drug for a specified indication.

OFF-LABEL USE: A drug prescribed for conditions other than those approved by the FDA.

OPEN-LABEL TRIAL: A clinical trial in which doctors and participants know which drug or vaccine is being administered.

ORPHAN DRUGS: An FDA category that refers to medications used to treat diseases and conditions that occur rarely. There is little financial incentive for the pharmaceutical industry to develop medications for these diseases or conditions. Orphan drug status, however, gives a manufacturer specific financial incentives to develop and provide such medications.

PEER REVIEW: Review of a clinical trial by experts chosen by the study sponsor. These experts review the trials for scientific merit, participant safety, and ethical considerations.

PHARMACOKINETICS: The processes (in a living organism) of absorption, distribution, metabolism, and excretion of a drug or vaccine.

PHASE I TRIALS: Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants and/or patients.

PHASE II TRIALS: Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

PHASE III TRIALS: Expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide and adequate basis for physician labeling.

PHASE IV TRIALS: Post-marketing studies to delineate additional information including the drug's risks, benefits, and optimal use.

PLACEBO: A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness. (See **Placebo Controlled Study**).

PLACEBO CONTROLLED STUDY: A method of investigation of drugs in which an inactive substance

(the placebo) is given to one group of participants, while the drug being tested is given to another group. The results obtained in the two groups are then compared to see if the investigational treatment is more effective in treating the condition.

PLACEBO EFFECT: A physical or emotional change, occurring after a substance is taken or administered, that is not the result of any special property of the substance. The change may be beneficial, reflecting the expectations of the participant and, often, the expectations of the person giving the substance.

PRECLINICAL: Refers to the testing of experimental drugs in the test tube or in animals - the testing that occurs before trials in humans may be carried out.

PREVENTION TRIALS: Refers to trials to find better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.

PROTOCOL: A study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment (See **Inclusion/Exclusion Criteria**).

QUALITY OF LIFE TRIALS (or Supportive Care trials): Refers to trials that explore ways to improve comfort and quality of life for individuals with a chronic illness.

RANDOMIZATION: A method based on chance by which study participants are assigned to a treatment group. Randomization minimizes the differences among groups by equally distributing people with particular characteristics among all the trial arms. The researchers do not know which treatment is better. From what is known at the time, any one of the treatments chosen could be of benefit to the participant (See **Arm**).

RANDOMIZED TRIAL: A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized. (See **Arm** and **Placebo**).

RECRUITING: The period during which a trial is attempting to identify and enroll participants. Recruitment activites can include advertising and other ways of solicting interest from possible particpants. (See **recruitment status** and **enrolling**).

RECRUITMENT STATUS: Indicates the current stage of a trial, whether it is planned, ongoing, or completed. Possible values include:

- Not yet recruiting: participants are not yet being recruited or enrolled
- Recruiting: participants are currently being recruited and enrolled
- Enrolling by invitation: participants are being (or will be) selected from a predetermined population
- Active, not recruiting: study is ongoing (i.e., patients are being treated or examined), but enrollment has completed
- Completed: the study has concluded normally; participants are no longer being examined or treated (i.e., last patient's last visit has occurred)
- Suspended: recruiting or enrolling participants has halted prematurely but potentially will resume
- Terminated: recruiting or enrolling participants has halted prematurely and will not resume; participants are no longer being examined or treated
- Withdrawn: study halted prematurely, prior to enrollment of first participant

RISK-BENEFIT RATIO: The risk to individual participants versus the potential benefits. The risk/benefit ratio may differ depending on the condition being treated.

SCREENING TRIALS: Refers to trials which test the best way to detect certain diseases or health conditions.

SIDE EFFECTS: Any undesired actions or effects of a drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental drugs must be evaluated for both immediate and long-term side effects (See **Adverse Reaction**).

SINGLE-BLIND STUDY: A study in which one party, either the investigator or participant, is unaware of what medication the participant is taking; also called single-masked study. (See **Blind** and **Double-Blind Study**).

SINGLE-MASKED STUDY: See **Single-Blind Study.**

STANDARD TREATMENT: A treatment currently in wide use and approved by the FDA, considered to be effective in the treatment of a specific disease or condition.

STANDARDS OF CARE: Treatment regimen or medical management based on state of the art participant care.

STATISTICAL SIGNIFICANCE: The probability that an event or difference occurred by chance alone. In clinical trials, the level of statistical significance depends on the number of participants studied and the observations made, as well as the magnitude of differences observed.

STUDY ENDPOINT: A primary or secondary outcome used to judge the effectiveness of a treatment.

STUDY TYPE: The primary investigative techniques used in an observational protocol; types are Purpose, Duration, Selection, and Timing.

SUSPENDED: See **Recruitment Status**

TERMINATED: See **Recruitment Status**

TOXICITY: An adverse effect produced by a drug that is detrimental to the participant's health. The level of toxicity associated with a drug will vary depending on the condition which the drug is used to treat.

TREATMENT IND: IND stands for Investigational New Drug application, which is part of the process to get approval from the FDA for marketing a new prescription drug in the U.S. It makes promising new drugs available to desperately ill participants as early in the drug development process as possible. Treatment INDs are made available to participants before general marketing begins, typically during Phase III studies. To be considered for a treatment IND a participant cannot be eligible to be in the definitive clinical trial.

TREATMENT TRIALS: Refers to trials which test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

WITHDRAWN: See **Recruitment Status**

Glossary Sources:

AIDSinfo: **Glossary of HIV/AIDS-Related terms 4th Edition.**
CenterWatch, Inc. Patient Resources: Glossary.
ECRI (formerly the Emergency Care Research Institute).
Eli Lilly and Company: Lilly Clinical Trials Glossary.
MediStudy.com Inc: ClinicalTrials: A-Z Glossary.
National Cancer Institute: **Cancer.gov Dictionary.**

Background Information

Last Updated: 2007/09/20

EXHIBIT 45

The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Rosiglitazone Maleate
Study No.: Study No.: ZM2005/00181/01 and Study No.: HM2006/00497/00 / WEUSRTP866
Title: Study No.: ZM2005/00181/01: Avandia Cardiovascular Event Modeling Project Study No.: HM2006/00497/00 / WEUSRTP866: Coronary Heart Disease Outcomes in Patients Receiving Antidiabetic Agents
Rationale: As part of GSK's ongoing pharmacovigilance program, an evaluation of the association (if any) between rosiglitazone (RSG) and cardiovascular events was undertaken for events of congestive heart failure (CHF) and for events related to myocardial ischemia. Two distinct approaches have been used in this evaluation. One approach examined events of CHF as well as events related to myocardial ischemia utilizing a retrospective statistical analysis of integrated clinical trials. The majority of patients in this analysis were randomized to a fixed dose of RSG added to background therapy vs maintenance of the background therapy alone. The second approach examined events related to myocardial ischemia (hospitalizations for myocardial infarction and/or coronary revascularization) utilizing a large, well-balanced retrospective observational study. Comparisons were made between matched cohorts of patients initiating antidiabetic therapy as oral monotherapy or oral dual therapy or combinations with insulin in which patients were treated in a US clinical practice environment.
Objectives (Integrated Clinical Trials): To estimate the risk expressed as point estimates and with the associated confidence intervals (CIs) of developing / exacerbating CHF and separately events associated with myocardial ischemia for RSG relative to active or placebo control in addition to background anti-diabetic therapies. The following treatment regimens were evaluated: RSG monotherapy (mono), RSG in combination with metformin (MET), RSG in combination with a sulfonylurea (SU), triple therapy (SU+MET+RSG) or RSG in combination with insulin. **Secondary:** To assess the value of various cardiac risk factors in predicting the occurrence of CHF or myocardial ischemia in the cohort of diabetic subjects examined in this statistical analysis. **Objectives (Observational Study):** **Primary:** To compare the incidence of myocardial infarction (MI) and coronary revascularization (CR) among adults with type 2 diabetes initiating rosiglitazone (RSG) compared with similar patients with type 2 diabetes who receive metformin (MET), sulphonylureas (SU), either as monotherapy or in combinations, including combinations with insulin. **Secondary:** To compare the incidence of myocardial infarction and coronary revascularization in adults with type 2 diabetes stratified by coronary heart disease (CHD) risk factors (i.e. No CHD, CHD with no dispensing of a nitrate, CHD plus at least one dispensing of a nitrate).
IndicationType 2 diabetes mellitus
Study Investigators/Centers: Study No.: ZM2005/00181/01: GSK Conducted Study Study No.: HM2006/00497/00 / WEUSRTP866: Conducted by i3Drug Safety
Research Methods:
Data Source (Integrated Clinical Trials): An initial statistical analysis was conducted on the cohort of type 2 diabetes mellitus (T2DM) subjects enrolled in the GlaxoSmithKline (GSK)-sponsored double-blind, controlled studies that utilized total daily doses of 4 milligrams (mg) or 8mg of RSG and had statistical analysis completed (SAC) on or before September 30, 2004. In total, this statistical analysis included data from 11,586 subjects from 37 controlled double-blind studies. Following the initial analysis, an additional exploratory recursive partitioning analysis was also conducted to assess whether any subgroup(s) of subjects appeared to be at particular risk for myocardial ischemic events. Further statistical analysis was conducted on an updated integrated dataset in order to assess the consistency of results with the initial analysis. The updated integrated dataset contained 5 additional clinical trials with SAC on or before August 2005 and included data from a total of 14,237 subjects from 42 controlled double-blind studies. This summary focuses on the results from the updated Integrated data analyses as it provides the largest and most recent dataset available. The results from the 2 datasets were generally similar. Any numerical differences were not clinically significant. **Data Source (Observational Study):** i3 Drug Safety has access to a proprietary research database of commercial enrollees of United Healthcare health plans who have both medical and prescription benefit coverage. The research database included complete health services utilization information (e.g., claims for all prescription dispensings, inpatient and outpatient services, and procedures including the associated diagnoses and costs) on about 12 million persons in

25 states in 2005. The database captures a longitudinal record of insurance claims for all paid medical services, irrespective of treatment site.

Study Design: Study No.: ZM2005/00181/01: Retrospective statistical analysis of integrated clinical trials
Study No.: HM2006/00497/00 / WEUSRTP866: Retrospective cohort study with propensity score matching.

Study Population (Integrated Clinical Trials):

- 14,237 subjects from 42 controlled double-blind studies (8604 RSG-treated, 5633 non-RSG)
- Subjects with CHF events (SAEs: 49, Serious or non-serious AEs: 104)
- Subjects with Myocardial Ischemia events (SAEs: 126, Serious or non-serious AEs: 256)

Study Population (Observational Study):

- Monotherapy group: 11,227 initiators of RSG were identified of whom 8,977 (80%) were matched to 8,977 initiators of metformin and 8,977 initiators of SU (total matched group size 26,931). The monotherapy group was followed for an average of 1.1 years (median follow-up = 0.8 years).
- Dual therapy group: 2,075 initiators of RSG plus SU were identified, of whom 1,362 (66%) were matched to 1,362 initiators of RSG plus metformin and 1,362 initiators of metformin plus SU (total matched group size 4,086). The dual therapy group was followed for an average of 1.2 years (median follow-up = 0.9 years).
- Combination-with-insulin group: 1,236 initiators of RSG in combination with insulin were identified, of whom 1,173 (95%) were matched to 1,173 initiators of other antidiabetic agents in combination with insulin (total matched group size 2,346). The combination with insulin group was followed for an average of 1.7 years (median follow-up = 1.4 years).
- Following matching, the frequency of all of the factors used in the propensity score matching process were well balanced across the groups.

Study Exposures, Outcomes:

Study Exposure (Integrated Clinical Trials)
Mean Duration of exposure to study medication (Integrated Clinical Trials)

Treatment Comparison (days, mean ± SD)	Treatment Group	
	RSG	CONTROL
RSG Mono vs. Placebo	133.4 ± 76.2	117.4 ± 87.0
RSG Mono vs. SU/MET Mono	226.1 ± 114.8	220.6 ± 105.7
MET+RSG vs. MET Mono	171.6 ± 61.7	168.8 ± 66.7
MET+RSG vs. MET+SU	189.4 ± 59.7	198.0 ± 65.3
SU+RSG vs. SU Mono	192.9 ± 121.5	187.0 ± 124.4
SU+MET+RSG vs. SU+MET	172.9 ± 54.2	174.0 ± 59.2
INS+RSG vs. INS Mono	157.7 ± 50.6	159.2 ± 49.3

Study Exposure (Observational Study): For the "as-balanced" (intent-to-treat) analyses, each patient was classified according to the drug use that defined his or her cohort entry.
For the "as-treated" (time-on-drug) analyses, patient exposure to the study drugs continued until follow-up ended. Subjects contributed follow-up time to the various regimens depending on whether each day of follow-up fell within the period defined by the days supply of each study drug dispensing.

Data Analysis Methods (Integrated Clinical Trials): An initial statistical analysis was conducted on the entire cohort of T2DM subjects enrolled in a total of 37 company-sponsored double-blind, controlled studies. The determination of events (CHF or myocardial ischemia) was based on a retrospective blinded review of narratives by a group of GSK physicians for serious adverse events (SAEs), and blinded review of the individual investigator-provided verbatim terms for non-serious events. For SAEs, all cases were reviewed by three GSK physicians and were also reviewed by an external cardiologist. The allocation of events was confirmed by the three GSK physicians and where there were differing opinions, a final decision was made by the external cardiologist.

The primary analysis for each regimen by control combination was based on SAEs. RSG 4mg and RSG 8mg doses were pooled for this analysis. The primary methodology for the initial dataset was the "full logistic regression analysis" which not only adjusted for the number of major CV risk factors (i.e. coronary heart disease (CHD), cerebrovascular disease, CHF and peripheral vascular disease) and exposure, but also permitted the inclusion of a number of other baseline factors as covariates in the model. The model determined the potential contribution of covariates to the endpoints of CHF and myocardial ischemia. An exact logistic regression, which requires fewer assumptions, was also pre-defined and performed as a secondary analysis as were the analyses for AEs. Point estimates and confidence

intervals for the odds ratio were generated to compare RSG vs control in 7 comparison strata.

Following the initial analysis, an additional exploratory recursive partitioning analysis for ischemic events was also conducted using the initial dataset to assess whether any subgroup(s) of subjects identified using baseline characteristics appeared to be at particular risk for myocardial ischemic events. The recursive partitioning methodology was considered exploratory in the sense that the subject subgroups were not pre-defined, but were determined by the data; i.e. recursive partitioning was used to generate a hypothesis rather than to confirm a hypothesis.

Data Analysis Methods (Observational Study):
Initiators of the antidiabetic medications RSG, MET and SU from July 2000 through December 2004 were identified and matched into cohorts of monotherapy, dual therapy, and combination therapy with insulin, using propensity score matching. Propensity score matching is a multivariate balancing procedure that balances the distribution of characteristics within each cohort that may have influenced a physician's choice of therapy for an individual patient, controlling for a number of sources of potential confounding. The cohorts were followed from July 2000 through December 2005. Since this represents a clinical practice setting, it is assumed that patients were treated according to the disease management algorithms used by the managed care organization.

"As-balanced" analyses (intent-to-treat) and "as-treated" analyses (time-on-drug) were conducted.
"As-balanced" analyses were performed for the first occurrence of MI, CR, and MI &/or CR. Kaplan-Meier curves were calculated for the first occurrence of each of the study outcomes in each cohort in the three study groups (monotherapy, dual therapy and combination with insulin). Each analysis provided hazard ratios as estimated from multivariate Cox proportional hazards models in each study group, adjusted for baseline covariates, for the following five pair-wise comparisons: RSG vs SU; RSG vs MET; RSG + MET vs SU + MET; RSG + SU vs SU + MET; RSG + Insulin vs Other-oral-antidiabetic-agents (excluding TZDs) + Insulin. The 'as-balanced" analysis was performed for the full follow-up and for the follow-up truncated at the six months from cohort entry, similar to the average follow-up in the integrated clinical trials.
In the "As-treated" analysis, Poisson regression was used to provide estimates of the relative incidence rates between current use periods for the above defined five pair-wise comparisons.
An analysis of RSG versus non-RSG exposure within coronary heart disease (CHD) risk factor strata ("No CHD," "CHD with no nitrates" and "CHD with nitrates") was also conducted.

Limitations (Integrated Clinical Trials) The clinical trials included in this retrospective analysis were not specifically designed to systematically collect or assess endpoints of CHF and myocardial ischemia. Importantly, for this analysis, none of the AEs recorded as CHF or relating to myocardial ischemia were prospectively adjudicated.

- Not all relevant information was systematically collected during the clinical trials.
- There were small numbers of events, thus limiting the ability of the statistical analysis to account for all possible contributing factors.
- Any dose response was not reliably estimated due to the small numbers of events.
- Analysis included only short-term studies (the majority were 6 months in duration) of differing designs, a variety of populations, and evolving medical practices.

Limitations (Observational Study)

- Although the population under study was large, the statistical power of this study was limited by the rarity of the outcomes, particularly in the shorter follow-up periods and in the smaller cohorts.
- The study population, which was comprised of insured and employed individuals, was under-representative of older, and unemployed or retired people, many of whom could be expected to have T2DM. This may have limited the extent to which the results from this study could be generalized to the elderly or uninsured.
- The analyses were based on exposure determined from pharmacy dispensing records. No documentation of actual compliance with prescribed therapy was available. The use of samples or other undocumented sources of medications was not available.
- Finally, there was the possibility that the results remained affected by unmeasured confounders (lifestyle factors such as body mass index, exercise, etc.), which have no surrogate in the administrative claims, even after the propensity score matching process. Although the propensity score matching was intended to balance the cohorts at baseline, we were not able to include direct clinical measures of T2DM severity or CHD risk, such as level of

glycemic control, blood lipid levels, body mass, exercise or smoking in matching the cohorts.

Study Results:

Demographic/Baseline Characteristics (Integrated Clinical Trials)

Total N (Integrated Clinical Trials)

Treatment Comparison	Treatment Group	
	RSG	CONTROL
RSG Mono vs. Placebo	1737	792
RSG Mono vs. SU/MET Mono	1127	1001
MET+RSG vs. MET Mono	1608	1419
MET+RSG vs. MET+SU	285	294
SU+RSG vs. SU Mono	2505	1926
SU+MET+RSG vs. SU+MET	597	310
INS+RSG vs. INS Mono	867	663
Total[1]	8604	5633

1. Data from a few subjects appeared in more than one of the seven treatment comparison strata. Therefore, the total number of subjects is fewer than the sum of subjects across the seven strata.

Number of Major Baseline Risk Conditions* - – Common Risk Factors for CHF and CHD (Integrated Clinical Trials)

Treatment Comparison (%, 0 / 1 / ≥2 risk conditions)	Treatment Group					
	RSG			CONTROL		
	0	1	≥2	0	1	≥2
RSG Mono vs. Placebo	80.7%	15.1%	4.2%	79.3%	17.4%	3.3%
RSG Mono vs. SU/MET Mono	79.7%	16.6%	3.7%	74.7%	17.7%	7.6%
MET+RSG vs. MET Mono	84.3%	11.9%	3.8%	81.7%	14.4%	3.9%
MET+RSG vs. MET+SU	75.4%	18.9%	5.6%	70.1%	20.4%	9.5%
SU+RSG vs. SU Mono	79.4%	15.3%	5.2%	76.8%	16.7%	6.5%
SU+MET+RSG vs. SU+MET	74.7%	17.1%	8.2%	70.6%	16.8%	12.5%
INS+RSG vs. INS Mono	72.4%	18.2%	9.3%	71.0%	21.3%	7.7%

*Major risk factors were defined to be any of the following: baseline CHD, cerebrovascular disease, peripheral vascular disease (PVD), and baseline CHF.

Number of CV Medications at Screening (Integrated Clinical Trials)

Treatment Comparison (%, 0 / 1 / ≥2 CV medications)	Treatment Group					
	RSG			CONTROL		
	0	1	≥2	0	1	≥2
RSG Mono vs. Placebo	39.5%	25.4%	35.1%	41.9%	24.9%	33.2%
RSG Mono vs. SU/MET Mono	41.2%	21.0%	37.8%	37.4%	21.5%	41.2%
MET+RSG vs. MET Mono	34.3%	23.8%	42.0%	35.7%	21.6%	42.7%
MET+RSG vs. MET+SU	14.7%	20.7%	64.6%	15.6%	20.1%	64.3%
SU+RSG vs. SU Mono	40.4%	21.2%	38.4%	37.5%	20.6%	41.9%
SU+MET+RSG vs. SU+MET	26.6%	23.1%	50.3%	25.5%	21.0%	53.5%
INS+RSG vs. INS Mono[1]	26.0%	22.0%	52.1%	25.2%	20.7%	54.3%

1. Note: The treatment sequence for the INS+RSG combination involved adding RSG to established INS therapy

Primary Outcome(s): (Integrated Clinical Trials)

CHF SAEs (Integrated Clinical Trials)

	Exact Logistic Analysis[1] – Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset Events / Subjects (%)	
Treatment Comparison	Initial Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo	0.24 (<0.01, 4.70)	0.25 (<0.01, 4.75)	1 / 1737 (0.06)	2 / 792 (0.25)
RSG Mono vs. SU/MET Mono	0.17 (0.00, 1.32)	0.23 (<0.01, 2.14)	1 / 1127 (0.09)	5 / 1001 (0.50)
MET+RSG vs. MET Mono	0.93 (0.00, 36.46)	0.95 (0.01, 75.20)	1 / 1608 (0.06)	1 / 1419 (0.07)
MET+RSG vs. MET+SU	0.60 (0.00, 8.28)	0.60 (0.00, 8.28)	0 / 285	2 / 294 (0.68)
SU+RSG vs. SU Mono	1.08(0.40, 2.95)	1.04(0.39, 2.86)	11 / 2505 (0.44)	9 / 1926 (0.47)
SU+MET+RSG vs. SU+MET	3.15 (0.35, 150.52)	3.15(0.35, 150.52)	5 / 597 (0.84)	1 / 310 (0.32)
INS+RSG vs. INS Mono	1.54(0.49, 5.68)	1.63(0.52, 6.01)	11 / 867 (1.27)	5 / 663 (0.75)

1. Covariates used in exact logistic regression: number of major CV risk factors.

Myocardial Ischemia SAEs (Integrated Clinical Trials)

Treatment Comparison	Exact Logistic Analysis[1] – Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset Events / Subjects (%)	
	Initial Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo	1.79 (0.59, 7.31)	2.03 (0.67, 8.24)	19 / 1737 (1.09)	4 / 792 (0.51)
RSG Mono vs. SU/MET Mono	1.63 (0.50, 5.78)	1.20 (0.46, 3.21)	11 / 1127 (0.98)	10 / 1001 (1.00)
MET+RSG vs. MET Mono	3.58 (0.71, 34.88)	3.33 (0.88, 18.63)	11 / 1608 (0.68)	3 / 1419 (0.21)
MET+RSG vs. MET+SU	1.03 (0.21, 4.48)	1.03 (0.21, 4.48)	4 / 285 (1.40)	6 / 294 (2.04)
SU+RSG vs. SU Mono	1.31 (0.67, 2.62)	1.08 (0.57, 2.07)	25 / 2505 (1.00)	19 / 1926 (0.99)
SU+MET+RSG vs. SU+MET	1.26 (0.29, 7.61)	1.26 (0.29, 7.61)	7 / 597 (1.17)	3 / 310 (0.97)
INS+RSG vs. INS Mono	2.23 (0.68, 9.52)	2.29 (0.69, 9.77)	12 / 867 (1.38)	4 / 663 (0.60)

1. Covariates used in exact logistic regression: number of major CV risk factors.

Secondary Outcome(s): (Integrated Clinical Trials)

All CHF AEs (Integrated Clinical Trials)

Treatment Comparison	Exact Logistic Analysis[1]—Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset: Events / Subjects (%)	
	Initial Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo	0.45 (<0.03, 6.22)	0.46 (0.03, 6.40)	2 / 1737 (0.12)	2 / 792 (0.25)
RSG Mono vs. SU/MET Mono	0.26 (0.03, 1.25)	0.38 (0.07, 1.48)	3 / 1127 (0.27)	11 / 1001 (1.10)
MET+RSG vs. MET Mono	0.55 (0.05, 4.90)	0.70 (0.10, 4.12)	3 / 1608 (0.19)	4 / 1419 (0.28)
MET+RSG vs. MET+SU	0.95 (0.08, 6.97)	0.95 (0.08, 6.97)	2 / 285 (0.70)	4 / 294 (1.36)
SU+RSG vs. SU Mono	1.53 (0.78, 3.12)	1.54 (0.79, 3.12)	27 / 2505 (1.08)	15 / 1926 (0.78)
SU+MET+RSG vs. SU+MET	4.36 (0.98, 40.00)	4.36 (0.98, 40.00)	13 / 597 (2.18)	2 / 310 (0.65)
INS+RSG vs. INS Mono	2.16 (0.88, 6.03)	2.26 (0.92, 6.29)	21 / 867 (2.42)	7 / 663 (1.06)

1. Covariates used in exact logistic regression: number of major CV risk factors.

All Myocardial Ischemia AEs (Integrated Clinical Trials)

Treatment Comparison	Exact Logistic Analysis[1] – Odds Ratio Point Estimate (95% CI)		Updated Integrated Dataset Events / Subjects (%)	
	Initial Integrated Data	Updated Integrated Data	RSG	Control
RSG Mono vs. Placebo	1.05 (0.52, 2.25)	1.15 (0.58, 2.46)	32 / 1737 (1.84)	12 / 792 (1.52)
RSG Mono vs. SU/MET Mono	1.21 (0.59, 2.53)	1.13 (0.60, 2.11)	25 / 1127 (2.22)	22 / 1001 (2.20)
MET+RSG vs. MET Mono	1.89 (0.67, 6.10)	2.72 (1.17, 7.03)	23 / 1608 (1.43)	8 / 1419 (0.56)
MET+RSG vs. MET+SU	1.25 (0.34, 4.47)	1.25 (0.34, 4.47)	6 / 285 (2.11)	7 / 294 (2.38)
SU+RSG vs. SU Mono	1.23 (0.80, 1.88)[2]	1.09 (0.72, 1.65)[2]	53 / 2505 (2.12)	39 / 1926 (2.02)
SU+MET+RSG vs. SU+MET	1.80 (0.55, 7.63)	1.80 (0.55, 7.63)	13 / 597 (2.18)	4 / 310 (1.29)
INS+RSG vs. INS Mono	2.02 (0.90, 4.94)	2.07 (0.93, 5.07)	24 / 867 (2.77)	9 / 663 (1.36)

1. Covariates used in exact logistic regression: number of major CV risk factors.
2. Computational burden for exact statistical methods increases with the number of events. Therefore, these results are from asymptotic analysis since the number of events is too large to allow computation of exact statistics.

Exploratory Analysis (Integrated Clinical Trials):

The recursive partitioning analysis identified three subgroups of subjects with lower, intermediate and higher levels of risk, respectively: subjects with no prior CHD, subjects with prior CHD who were not treated with nitrates at screening, and subjects with prior CHD who were treated with nitrates at screening. The incidence of myocardial ischemic events in subjects with a history of CHD concurrently taking nitrates was then determined using data from both the initial and the updated integrated datasets. Results from the two datasets were consistent.

Myocardial Ischemia all AEs (serious and non-serious) – Results from Proportional Hazards Regression in Recursive Partitioning Subgroups (Integrated Clinical Trials)

Recursive Partitioning Subgroup	Proportional Hazards Regression—Hazard Ratio Point Est. (95% CI)		Updated Integrated Dataset: Events / Patients (%)	
	Initial Integrated Data	Updated Integrated Data	RSG	Control
No pre-existing CHD	1.25	1.42	81 / 7395	36 / 4788

	(0.84, 1.87)	(0.96, 2.11)	(1.10%)	(0.75%)
Pre-existing CHD, no nitrates	1.08 (0.67, 1.74)	1.06 (0.68, 1.65)	47 / 886 (5.30%)	33 / 622 (5.31%)
Pre-existing CHD, with nitrates	2.45 (1.34, 4.49)	2.14 (1.20, 3.81)	43 / 323 (13.31%)	16 / 223 (7.17%)
Overall	1.29 (0.99, 1.69)	1.31 (1.01, 1.70)	171 / 8604 (1.99%)	85 / 5633 (1.51%)

Overall, the statistical analysis conducted on the updated integrated dataset demonstrated the consistency of results with the initial dataset. Only exact logistic regression analyses were performed in the updated integrated dataset, as some of the assumptions for the full logistic regression were not supported by the data in the initial integrated dataset.

Primary Outcome(s): (Observational Study)

Composite Outcome (MI/CR) results for the "as balanced" analysis (Observational Study)

Treatment regimen	Person years	Rate per 1000 person years (95%CI)	Reference Group	Composite Outcome HR(95% CI) RSG vs. Comparator For full follow-up	Composite Outcome HR(95% CI) RSG vs. Comparator for 6 month follow-up
N=8977					
Met mono	10,722	13.9 (11.8-16.3)			
SU mono	9772	19.5 (16.9-22.5)			
RSG mono	9676	15.7 (13.4-18.4)	Met	1.1 (0.9-1.3)	1.2 (0.9-1.8)
RSG mono			SU	0.8 (0.7-1.0)	0.8 (0.6-1.1)
N=1362					
Met+SU	1852	19.4 (13.8-26.6)			
RSG+Met	1683	14.3 (9.4-20.9)	Met+SU	0.8 (0.5-1.3)	1.1 (0.5-2.4)
RSG+SU	1474	26.5 (19.1-35.8)	Met+SU	1.3 (0.8-2.0)	1.7 (0.9-3.5)
N=1173					
RSG+insulin	1997	22.0 (16.2-29.3)	Other+Ins	0.9 (0.6-1.3)	1.0 (0.5-2.0)
Other oral+insulin	1957	26.1(19.6-34.0)			

N=number matched; HR=hazard ratio

Composite Outcome (MI/CR) results for the "as treated" analysis (Observational Study)

Treatment regimen	Person years	Rate per 1000 person years (95%CI)	Reference Group	Composite Outcome RR*(95% CI) RSG vs. Comparator
Met mono	6256	13.6 (10.9-16.8)		
SU mono	5631	23.1 (19.3-27.4)		
RSG mono	5650	17.5 (14.2-21.3)	Met	1.2 (0.9-1.6)
RSG mono			SU	0.8 (0.6-1.0)
Met+SU	927	17.3 (9.9-28.0)		
RSG+Met	841	17.8 (10.0-29.4)	Met+SU	1.1 (0.5-2.1)
RSG+SU	691	33.3 (21.1-49.9)	Met+SU	1.8 (0.9-3.4)
RSG+insulin	937	22.4 (13.9-34.3)	Other+Ins	0.6 (0.3-1.2)
Other oral+insulin	1465	29.4(21.3-39.6)		

*RR=relative risk

Secondary Outcome(s): (Observational Study)

Hazard rate ratios for composite outcome (MI/CR) stratified by presence or absence of CHD and nitrate use (Observational Study)

	Full Follow Up	Six month follow-up

		HR (95% CI)	
No CHD	RSG	0.98 (0.80-1.19)	1.13 (0.82 – 1.55)
	Non-RSG	Ref	Ref
CHD no nitrates	RSG	1.11 (0.79-1.58)	1.31 (0.80 – 2.14)
	Non-RSG	Ref	Ref
CHD with nitrates	RSG	0.48 (0.30-0.75)	0.46 (0.25-0.86)
	Non-RSG	Ref	Ref

Key Differences Between Integrated Clinical Trials and the Observational Balanced Cohort Study

	Integrated Clinical Trials	**Observational Balanced Cohort Study**
Events Analyzed	Myocardial Ischemia, including serious and non-serious events	Hospitalizations for: Myocardial infarction Coronary revascularization
Comparisons	Primarily add-on/placebo	Active Control
Treatment Progression	Washout of background treatment Background oral anti-hyperglycemic diabetic medication (OAD) maximized	Per clinical practice
Dosing	Primarily fixed dose or forced titration	Per clinical practice
Duration of Treatment	6 month average	Average >1 year
Method for Balancing Treatment Groups	Randomization	Propensity Score Matching

Conclusion:

Congestive Heart Failure (CHF):
The observations regarding CHF and RSG therapy remain consistent with previous observations from individual and integrated controlled clinical trials of an increased incidence of CHF in patients receiving RSG in insulin or sulfonylurea combinations.

Myocardial Ischemia:
Evaluation of events related to myocardial ischemia utilizing the two approaches described provided observations that are not entirely consistent with each other.

The data relating to myocardial ischemia from the integrated clinical trials analysis confirms that during relatively short studies of 6 months duration, the incidence of events of myocardial ischemia was low across all treatment groups. Although point estimates were modestly elevated with broad confidence intervals, based on the individual treatment group comparisons, no definitive conclusion can be drawn regarding the risk for developing myocardial ischemic events. Combining data from all treatment strata, the incidence of myocardial ischemic events in the RSG group was 1.99% and in the control group was 1.51%, with a hazard ratio of 1.31 (95% CI 1.01-1.70). An exploratory recursive partitioning analysis generated the hypothesis that patients with CHD and receiving nitrates could potentially be at increased risk of an event related to myocardial ischemia when taking RSG.

Data from the observational study suggested that in a clinical practice setting and over an average of one year follow-up, there was no excess risk for MI or coronary revascularization associated with RSG therapy either generally or in the CHD with nitrates group. For all the "as balanced" cohorts combined, and after adjustment for age group, gender, cost, hyperlipidemia, nitrates and cohort origin, the incidence of the composite endpoint of MI and/or CR was 17.5 events per 1000 person years for rosiglitazone containing regimens and 17.6 events per 1000 person years for other anti-diabetic agents [HR 0.93 (95% confidence interval 0.80 - 1.10)].

The nature of the relationship between RSG therapy and events related to myocardial ischemia remains unclear due to the inconsistencies in the results provided by these two approaches.

Publications:
No publication

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